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*EDITORS*

# Pediatric Hypertension

*Fourth Edition*

 Springer

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Joseph T. Flynn • Julie R. Ingelfinger  
Karen M. Redwine  
Editors

# Pediatric Hypertension

Fourth Edition

With 94 Figures and 97 Tables

 Springer

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## Preface to the Fourth Edition

We are delighted to present this expanded fourth edition of *Pediatric Hypertension*, which is intended to capture and update the ongoing progress in childhood hypertension. There is a growing recognition that adult cardiovascular disease has its origins in childhood, supported by many recent studies. Additionally, the assessment of the short-term sequelae of childhood hypertension is providing new and important data, reviewed herein. Further, there are increasing numbers of studies that are delineating mechanisms of blood pressure elevation in the young. While the obesity epidemic appears to be leveling off (at least in the United States), it remains an important contributor to the higher prevalence of childhood hypertension reported in recent years; numerous epidemiologic studies have become available since publication of the third edition of this text and are detailed here. With publication of this new fourth edition, we hope to bring further focus on the importance of understanding and addressing the role of the obesity epidemic in pediatric hypertension.

As our publisher, Springer, has transitioned this text to its Major Reference Work program, which is available not only in print but also online, which allows for continual updating, we have been able not only to retain the topics covered in previous editions of *Pediatric Hypertension* but also to add new chapters that address additional and important aspects of childhood hypertension. One new chapter addresses the controversy over routine childhood blood pressure screening raised by the 2014 US Preventive Services Task Force Report. Obesity hypertension is now covered in two chapters, one focusing on mechanisms and the other on clinical aspects. Another important mechanism of cardiovascular disease, vascular dysfunction, is covered in a new chapter in the first section of the text. We also now address the important topic of home blood pressure measurement, while continuing to cover casual and ambulatory blood pressure measurement in detail. Expanded chapters on ESRD-related hypertension, substance-induced hypertension, hypertension in oncology patients, and hypertension in young adults should be of substantial interest to clinicians who care for such patients. We have also expanded the section on hypertension research with a new chapter on cohort studies and meta-analyses and their role in studying childhood hypertension. Finally, we have added a short Appendix summarizing the major changes of the 2017 American Academy of Pediatrics clinical practice guideline on childhood hypertension, which was completed as this new edition was in progress.

It is impossible to put together a comprehensive text such as *Pediatric Hypertension* without more than “a little help from our friends.” We are greatly indebted to our returning authors as well as to our new authors, all of whom were asked to contribute to the text because of their acknowledged expertise in childhood hypertension. We also thank Daniela Graf and Rebecca Urban from Springer for helping keep everyone on task. We are certain that you will agree that the tremendous amount of work that has been devoted to this edition of *Pediatric Hypertension* has led to a comprehensive and useful text, which we hope you will consult often in your clinics and research laboratories.

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## Preface to the Third Edition

We are excited to offer you this third edition of *Pediatric Hypertension*. Interest in childhood hypertension has increased markedly since the publication of the prior editions of this text, fueled in part by the increase in the prevalence of hypertension in children and adolescents, owing to the obesity epidemic. Investigators have continued to explore many aspects of hypertension in the young, resulting in better understanding of the mechanisms, manifestations and management of this important clinical problem. Cardiovascular disease remains the leading medical cause of death in the world. Only by understanding important risk factors such as hypertension at the earliest stages of disease, during childhood, can substantial progress at eradicating this disease be made.

In this edition, we have retained most of the topics from the prior two editions, but have made some important additions and replacements that we feel will increase the usefulness of the text to clinicians and researchers alike. New clinically oriented chapters on obesity-related hypertension, endocrine hypertension and renovascular hypertension should help guide the evaluation and management of these major causes of hypertension in the young. A new chapter on models of hypertension should help both researchers and clinicians to better understand the investigative approaches that have been employed to study childhood hypertension. There are also new chapters on hypertension in pregnancy and ethnic influences on hypertension in the young, which should be of particular interest to those who care for large numbers of teens and minority patients, respectively.

A text such as this would not have been possible without contributions from many busy people, all of whom are acknowledged experts in the field. We are profoundly grateful to our colleagues who agreed to contribute chapters to this text, especially those who willingly took on new topics only 2–3 years after

writing their chapters for the second edition! It has been a privilege to work with such a talented and generous group of collaborators, and we are sure that you will agree that their efforts have resulted in an enhanced third edition.

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## Preface to the Second Edition

Interest in pediatric hypertension dates back nearly half a century, when it was first recognized that a small percentage of children and adolescents had elevated blood pressures – and in those days, the same normal values for adult blood pressure were utilized in children! The many advances since that time have led to a much clearer understanding of how to identify, evaluate, and treat hypertensive children and adolescents. At the same time, many questions remain: What causes hypertension in children without underlying systemic conditions? What are the long-term consequences of high blood pressure in the young? What is the optimal therapy of childhood hypertension? and Does such treatment benefit the affected child or adolescent? Can we identify children at risk of developing hypertension and intervene to prevent its occurrence? Readers conversant with the history of hypertension in the young will recognize that these questions were being asked decades ago and may still be unanswered for many years to come.

The first text focusing on pediatric hypertension was published in 1982. The book you are about to read is a direct descendant of that first effort to summarize what is known about hypertension in the young. We are fortunate to have been given the first opportunity to produce a second edition of such a text, which reflects the increased interest in hypertension in the young that has developed since the publication of the first edition of *Pediatric Hypertension*. Many chapters from the first edition have been revised and updated by their original authors; others have been written by new authors. New chapters on topics of recent interest in pediatric hypertension such as the metabolic syndrome and sleep disorders have been added. We hope that the reader will find this new edition of *Pediatric Hypertension* to be an up-to-date, clinically useful reference as well as a stimulus to further research in the field.

It is also our hope that the advances summarized in this text will ultimately lead to increased efforts toward the prevention of hypertension in the young, which, in turn, should ameliorate the burden of cardiovascular disease in adults. We thank our many colleagues who have taken time from their busy

schedules to contribute to this text – and we are sure that you will agree with us that their combined efforts have resulted in a valuable reference to those interested in hypertension in the young.

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## Preface to the First Edition

More than a quarter of a century has elapsed since the first Task Force on Blood Pressure Control in Children was published in 1977. Since that seminal publication, normative data have been obtained for both casual and ambulatory children's blood pressure. Blood pressure measurement in infants, children, and adolescents, once an afterthought, has become routine. *Pediatric Hypertension* discusses the many aspects of pediatric hypertension – a multidisciplinary subspecialty that is comprised of pediatric nephrologists, cardiologists, endocrinologists, pharmacologists, and epidemiologists. Although some areas of our discipline have become well established, others, such as routine use of ambulatory blood pressure recording and well-designed trials in pediatric hypertension, are still emerging. Accordingly, we have included chapters that focus on aspects of blood pressure control and hypertension in the very young that are particularly relevant to those caring for infants, children, and adolescents.

*Pediatric Hypertension* opens with chapters concerning blood pressure regulation in the very young: the transition from fetal life to infant circulation, the factors that regulate blood pressure in early childhood, and the chronobiology of pediatric blood pressure. We then move on to the assessment of blood pressure in children. The book addresses both casual and ambulatory blood pressure measurement methodologies and norms, as well as the epidemiology of hypertension in children.

Definitions of hypertension in children, predictors of future hypertension, risk factors, and special populations are discussed at length. Comprehensive chapters on both primary and secondary hypertension in children point out differences in presentation of hypertension in the pediatric, in comparison to the adult, population. The contributions of genetics to the understanding of hypertension are presented, as well as those events during gestation and perinatal life that may influence the development of later hypertension. Risk factors that are discussed include the influences of race and ethnicity, diet, obesity, and society. Special populations, including the neonate with hypertension and the child with chronic renal failure or end-stage renal disease, are each discussed in a separate chapter. In those chapters, the pathophysiology insofar as it is known is also considered.

This text concludes with a section that focuses on the evaluation and management of pediatric hypertension. Suggestions for evaluation are presented, and both nonpharmacologic and pharmacologic therapy are discussed

at length. The 1997 Food and Drug Administration Modernization Act, which offers extension of market exclusivity in return for approved clinical trials of medications with pediatric indication, has had a major impact on the conduct of pediatric antihypertensive medication trials. The current status of such pediatric antihypertensive trials is presented. In the appendix, the reader will find the latest tables for the definition of hypertension in children from the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents, to be published in *Pediatrics* in the summer of 2004.

We hope that *Pediatric Hypertension* provides a catalyst for more interest in pediatric hypertension as well as a guide for the interested clinician or clinical researcher already active in this discipline. Very shortly, the results of additional trials concerning new antihypertensive agents in children will be available with the mandate that new antihypertensive medications be evaluated in children. An update by the Task Force on Blood Pressure Control in Children will also be completed in 2004. A number of groups that have a special interest in blood pressure and its control in the very young will continue to contribute to the field, among them, most notably, the International Pediatric Hypertension Association; the National Heart, Lung, and Blood Institute; the American Society of Hypertension; and the American Society of Pediatric Nephrology. These initiatives will lead to a better understanding of the definition, causes, consequences, prevention, and treatment of pediatric hypertension. In addition to advances in molecular and genetics laboratories, new technologies in assessment of human cardiac and vascular anatomy and physiology will help to elucidate the pathophysiology of hypertension and its response to management. In so doing, our hope is that the trend towards reduction in cardiovascular morbidity and mortality will continue for the current generation of children.

Finally, we wish to acknowledge the pioneering work of so many in the field of pediatric hypertension that has given us the foundation and tools to advance our field.

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International Pediatric Hypertension Association

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**Part I**

**Regulation of Blood Pressure and  
Pathophysiologic Mechanisms of  
Hypertension**

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# Neurohumoral and Autonomic Regulation of Blood Pressure

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## Abstract

Interacting neural, hormonal, and metabolic mechanisms act locally and systemically to regulate cardiovascular function. This chapter discusses the basic physiological mechanisms of the neurohumoral and autonomic contributions to blood pressure regulation. Much that we will present about these mechanisms stems from studies in experimental animal models. Differential rates of maturation of these systems affect their ability to maintain blood pressure and delivery of oxygen and nutrients at specific times of life. This chapter outlines autonomic control of the fetal and postnatal cardiovascular system, particularly highlighting developmental changes in arterial baroreflex, cardiopulmonary reflex, and chemoreflex function. Additionally, humoral factors that act within the central and peripheral nervous system to influence sympathovagal balance will be discussed.

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## Keywords

Autonomic • Baroreflex • Blood pressure • Fetus • Parasympathetic • Sympathetic

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## Introduction

Cardiovascular homeostasis is mediated through interacting neural, hormonal, and metabolic mechanisms that act both centrally and locally. These basic physiological mechanisms, which have been extensively studied in the adult, are functional early during development, although

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differential rates of maturation of these systems influence their ability to maintain arterial blood pressure, organ blood flow, and delivery of oxygen and nutrients. The autonomic nervous system, classically divided into the sympathetic and parasympathetic nervous systems, poses a first-line defense against challenges to the cardiovascular system, such as hypotension, blood loss, and hypoxia. Sympathetic innervation of the heart and blood vessels is excitatory, causing increases in heart rate, cardiac contractility, and vasoconstriction. In contrast, parasympathetic innervation (vagal) is inhibitory, decreasing heart rate and contractility. While it remains unclear where long-term regulation of blood pressure resides (kidney, brain, or both), responses from powerful monitors of acute changes in arterial pressure, baroreceptors, and of oxygen content and pH, chemoreceptors, are vital for maintaining circulatory function. These neural pathways are modulated by a number of endocrine and paracrine factors, including angiotensin II, arginine vasopressin, and glucocorticoids. Understanding the neurohumoral mechanisms participating in cardiovascular regulation during the fetal and postnatal development, particularly as they relate to the physiological adaptations occurring with the transition from fetal to newborn life, is important.

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## Overview of Autonomic Function

### Vasoactive Sites in the Brain

Simplistically, arterial blood pressure is determined by total peripheral resistance, blood volume, and cardiac output. Peripheral resistance and cardiac output are governed by interacting neural, hormonal, and metabolic mechanisms signaling within the brain, end organs, and the vasculature. The central nervous system is particularly critical for cardiovascular homeostasis, as autonomic tone to the heart and vasculature is continuously modulated by afferent signals from the arterial baroreceptors and chemoreceptors acting upon cardiovascular centers within the brain. These

centers, located between afferent and efferent pathways of the reflex arc, integrate a variety of visceral and behavioral inputs and in turn modulate a wide range of cardiovascular and metabolic responses (Spyer 1994). Studies using a number of investigational approaches identified that afferent fibers from baroreceptors and chemoreceptors, located within the carotid sinus, aortic arch, and carotid bodies, travel with the glossopharyngeal and vagal nerve and terminate within the medullary nucleus tractus solitarius (NTS) (Dampney et al. 2002). Second-order neurons originating from the NTS project to cardiac vagal motoneurons in the nucleus ambiguus and interneurons in the caudal ventrolateral medulla (VLM). Neurons that express a lot of gamma-aminobutyric acid (GABAergic neurons) from this area project to and inhibit sympathetic premotor neurons in the rostral ventrolateral medulla. Sympathetic neurons in the rostral VLM are tonically active, projecting to the intermediolateral cell column of the spinal cord and playing a critical role in maintaining sympathetic vasomotor tone.

Important components of central neural control of the cardiovascular system include inputs from higher brain centers that integrate other intrinsic and extrinsic factors to regulate sympathetic and vagal activity. For example, specialized central nervous system structures, the circumventricular organs (subfornical organ, organum vasculosum lamina terminalis), lack a blood-brain barrier and are able to sense peripheral signals, such as circulating angiotensin II, and transmit information via neural projections to medullary and hypothalamic autonomic control centers, such as the supraoptic nucleus and paraventricular nucleus reviewed in Smith and Ferguson (2010) and Dampney (2016). Additional brain centers provide central command of cardiovascular responses that do not require input from peripheral receptors. A common example is the cardiovascular response to acute psychological stressors (defensive behaviors). Receiving inputs from the cortex, thalamus, and hippocampus, the amygdala plays a critical role in generating and coordinating cardiovascular responses to alerting stimuli.

## Tonic Autonomic Activity

Tonic discharge of postganglionic sympathetic neurons is an important regulator of vasomotor tone and ultimately, arterial pressure. In adults, sympathetic activity can be assessed using direct measurement of muscle sympathetic nerve activity (MSNA) as well as norepinephrine spillover and plasma norepinephrine levels. In young adult men, MSNA measured at rest can vary from five- to tenfold, though is inversely related to cardiac output (Charkoudian et al. 2005; Charkoudian and Rabbitts 2009). Causes of the interindividual variability are not known, though identical twins display similar MSNA values, suggesting a strong genetic component (Wallin et al. 1993). Interestingly, the relation between MSNA, cardiac output, and peripheral resistance are not seen in adult women (Hart et al. 2009). Total peripheral resistance is highly correlated with MSNA, and the fall in blood pressure during ganglionic blockade is proportional to resting MSNA and plasma norepinephrine concentration (Jones et al. 2001). Men with high MSNA displayed a greater increase in blood pressure following systemic nitric oxide synthase inhibition, suggesting those with high levels of MSNA may be at increased risk of hypertension with even a modest decrease in endothelial function (Charkoudian et al. 2006). Whole-body sympathetic activity, reflected by increases in MSNA and norepinephrine levels, increases with aging in adults (Joyner et al. 2010).

Though human data are lacking, animal studies suggest that the contribution of sympathetic drive to blood pressure changes during early development as well. The hypotensive response to ganglionic blockade may be used as an index of the neurally mediated contribution to blood pressure. Both alpha-adrenergic and ganglionic blockade, which inhibit end-organ responses to noradrenaline and sympathetic transmission at the ganglia, respectively, produce greater decreases in blood pressure in term fetal sheep than in preterm fetal sheep or newborn lambs, suggesting that fetal sympathetic tone is relatively high late in gestation (Tabsh et al. 1982; Vapaavouri et al. 1973). This hypotensive

effect continues to decline with postnatal development (Vapaavouri et al. 1973). Sympathetic nerve efferents co-release norepinephrine and neuropeptide Y (NPY) from sympathetic varicosities, both of which exert potent pressor effects (Sanhueza et al. 2003). The peripheral vasoconstrictor effect resulting from sympathetic outflow is likely fine-tuned by opposing vasodilator influences, such as nitric oxide (NO). Whether sympathetic noradrenergic and peptidergic tone is more pronounced in late fetal life while nitric oxide dilation is enhanced postnatally is not known. In rats, the sympathetic nervous system appears much more immature at birth compared to sheep as ganglionic blockade in the first 24–36 h of life has no effect on resting blood pressure (Mills and Smith 1986). At an early age, ganglionic transmission appears to be the rate-limiting step in efferent sympathetic control, as the pressor response to tyramine, which stimulates norepinephrine release, is minimal. On the other hand, the vascular sensitivity to alpha-adrenoreceptor stimulation is enhanced immediately after birth, likely an adrenergic compensatory response.

Arterial pressure displays natural oscillations within a physiological range, the degree of which is similar in fetal and postnatal life (Alper et al. 1987; Barres et al. 1992; Segar et al. 1994c; Yardly et al. 1983). In the adult, ganglionic blockade increases low-frequency arterial pressure variability, suggesting that a component of arterial pressure lability is peripheral or humoral in origin and is buffered by autonomic functions (Alper et al. 1987; Robillard et al. 1986). In contrast, ganglionic blockade in term fetal sheep significantly attenuates heart rate and arterial pressure variability, while spontaneous changes in fetal renal sympathetic nerve activity (RSNA) correlate positively with fluctuations in heart rate and arterial pressure, suggesting blood pressure oscillations are driven by, rather than buffered by, autonomic activity (Segar et al. 1994c). RSNA shows entrainment or rhythmicity with diastole in preterm, term, and adult sheep, though the delay between the diastolic nadir and the next peak in RSNA significantly decreases with

maturation (Booth et al. 2011a). Burst frequency also increased in term compared to preterm sheep and became sleep state dependent. Fetal sympathetic activity, heart rate, arterial pressure, and catecholamine levels are highest during periods of high-voltage, low-frequency electrocortical activity, suggesting oscillations in sympathetic tone are related to changes in the behavioral state of the fetus (Booth et al. 2011a; Clapp et al. 1980; Jensen et al. 2009; Mann et al. 1974; Reid et al. 1990; Wakatsuki et al. 1992). Other physiological parameters, including organ blood flows, regional vascular resistances, and cerebral oxygen consumption, are also dependent on electrocortical state and likely reflect changes in autonomic activity (Clapp et al. 1980; Jensen et al. 1986; Richardson et al. 1985).

The influence of the parasympathetic nervous system on resting heart rate appears to increase with maturation (Walker et al. 1978). Analysis of heart rate variability of fetal baboons 120–165 days of gestation suggests parasympathetic modulation is enhanced with advancing gestation (Stark et al. 1999). Cholinergic blockade produces no consistent effect of heart rate in premature fetal sheep, a slight increase in heart rate in term fetuses, and the greatest effect in lambs beyond the first week of life (Nuwayhid et al. 1975; Vapaavouri et al. 1973; Woods et al. 1977). In humans, heart rate decreases from birth to 16 years of age, implying ongoing vagal maturation during childhood and adolescence.

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## Arterial Baroreflex

The arterial baroreflex plays a critical role in the short-term regulation of arterial pressure. Acute changes in vascular stretch related to alterations in blood pressure modify the discharge of afferent baroreceptor fibers located in the carotid sinus and aortic arch. Following central integration of these changes in afferent nerve traffic, efferent parasympathetic and sympathetic nerve activities are altered to influence heart rate and peripheral vascular resistance and buffer changes in arterial pressure (Abboud and Thames 1983; Persson et al. 1989). For example, a decrease in blood

pressure results in a decrease in the baroreceptor firing rate, resulting in an increase in sympathetic vasomotor activity, and increase peripheral vascular resistance along with a decrease in cardiac vagal activity, resulting in increased cardiac output. Baroreflex control of heart rate is dominated by changes in cardiac vagal tone, although integrity of the reflex depends on both sympathetic and parasympathetic pathways (Yu and Lumbers 2000). Animal studies demonstrate that the arterial baroreflex is functional during fetal and early postnatal life (Booth et al. 2009; Brinkman et al. 1969; Itskovitz et al. 1983; Walker et al. 1978; Yardly et al. 1983). The observation that sinoaortic denervation produces marked fluctuations in fetal arterial pressure and heart rate further suggests the importance of the baroreflex to cardiovascular homeostasis in early development (Itskovitz et al. 1983; Yardly et al. 1983).

Single-fiber recordings of baroreceptor afferents in fetal, newborn, and adult animals demonstrate that carotid sinus nerve activity is phasic and pulse synchronous and that activity increases with a rise in arterial or carotid sinus pressure (Biscoe et al. 1969; Blanco et al. 1988a; Downing 1960; Ponte and Purves 1973; Tomomatsu and Nishi 1982). The threshold for carotid baroreceptor discharge is lower, and the sensitivity of baroreceptors to increases in carotid sinus pressure is greater in fetal than in newborn and 1-month-old lambs (Blanco et al. 1988a) and in newborn compared to adult rabbits (Tomomatsu and Nishi 1982). These findings suggest that any reduced heart rate responses to changes in arterial pressure during fetal life are not due to immaturity of afferent activity of baroreceptors but to differences in central integration and efferent pathways. The mechanisms regulating the changes in sensitivity of the baroreceptors early in development have not been investigated but may be related to changes in the degree of mechanical deformation of nerve endings and thus strain sensitivity, ionic mechanisms that operate at the receptor membrane to cause hyperpolarization, or substances released from the endothelium, including prostacyclin and nitric oxide, which modulate baroreceptor activity (Andresen 1984; Chapleau et al. 1988, 1991; Heesch et al. 1984; Jimbo et al. 1994;

Matsuda et al. 1995). Many but not all studies in fetal and newborn animals describe baroreflex sensitivity, determined by the heart rate response to alterations in blood pressure, being decreased early in development (Bauer 1939; Dawes et al. 1980; Shinebourne et al. 1972; Vatner and Manders 1979; Young 1966). Heart rate responses to increases and decreases in blood pressure in the premature sheep fetus appear to be asymmetric, being more sensitive to an increase than a decrease in blood pressure (Booth et al. 2009). In contrast to findings in sheep, the sensitivity of the cardiac baroreflex is greater in the horse fetus at 0.6 of gestation than at 0.9 of gestation (O'Connor et al. 2006).

Developmental changes in the cardiac baroreflex continue postnatally. Heart rate responses to pharmacologically induced increases and decreases in blood pressure in fetal ( $135 \pm 2$ -day gestation, term 145 day), newborn, and 4–6-week-old sheep demonstrated a tendency for the sensitivity of baroreflex control of heart rate to decrease with maturation (Segar et al. 1992). Other studies in sheep (Vatner and Manders 1979) and other species (Buckley et al. 1976; Gootman 1991) have found increasing cardiac baroreflex sensitivity with postnatal age. Reflex bradycardia in response to carotid sinus stimulation is absent in the newborn piglet, although vagal efferents exert a tonic action on the heart at this stage of development (Buckley et al. 1976). Age-related changes in heart rate in response to phenylephrine are also greater in 2-month-old piglets than in 1-day-old animals (Gootman 1991). Differences in species, experimental conditions, and developmental changes in the innervation and functional contributions of the two arms of the autonomic nervous system likely contribute to these reported differences.

Developmental changes in baroreflex control of sympathetic outflow, primarily measured as renal sympathetic nerve activity (RSNA) responses to increases and decreases in blood pressure, have been examined. In chronically instrumented preterm fetal sheep (0.7 of gestation), baroreflex control RSNA was absent although pulse-synchronous bursts of RSNA were present (Booth et al. 2009). This same group demonstrated in slightly older sheep (123 days or 0.83 of gestation) that baroreflex-mediated

inhibition but not excitation of RSNA was present (Booth et al. 2011b). This lack of sympathetic response to hypotension may have important implications in the ability of the fetus (or preterm infant) to adapt to low blood pressure. In studies of late-gestation fetal, newborn, and 4–6-week-old sheep, renal sympathoexcitation was present in response to hypotension, and in fact the sensitivity of the RSNA baroreflex function curve was greatest in the fetus and decreased during the postnatal period (Segar et al. 1992). Interestingly, studies in aging animals have shown that baroreflex control of heart rate and sympathetic nerve activity is impaired with senescence (Hajduczuk et al. 1991b). Thus, the sensitivity of the baroreflex likely increases with early maturation, reaching a maximum sensitivity occurring during some developmental period, and then decreases with advancing age, an effect that may contribute to the development of hypertension.

## Resetting of the Arterial Baroreflex

Resetting of the arterial baroreflex is defined as a change in the relation between arterial pressure and heart rate or between pressure and sympathetic and parasympathetic nerve activities (Chapleau et al. 1988, 1991). With sustained changes in blood pressure, the operating range of the baroreceptors shifts, or resets, in the direction of the prevailing arterial pressure. This shift in the range of blood pressure over which the baroreflex remains functional allows for the naturally occurring increase in blood pressure during fetal life, immediately after birth, and postnatal maturation (Segar et al. 1994a). The mechanisms regulating developmental changes in baroreflex sensitivity and controlling the resetting of the baroreflex are poorly understood. Basal discharge of baroreceptor afferents does not change during fetal and postnatal maturation, despite a considerable increase in mean arterial pressure during this time, indicating that baroreceptors reset during development, continuing to function within the physiologic range for arterial pressure (peripheral resetting) (Blanco et al. 1988a; Tomomatsu and Nishi 1982). Changes in the relation between

arterial pressure and sympathetic activity or heart rate may additionally result from altered coupling within the central nervous system of afferent impulses from baroreceptors to efferent sympathetic or parasympathetic activities (central resetting) and at the end organ (Chapleau et al. 1988). Locally produced factors, such as nitric oxide, and circulating hormones and neuropeptides, such as ANG II (AVP), activate additional neural reflex pathways that may modulate the changes in arterial baroreflex during development (Bishop and Haywood 1991).

While well established that the arterial baroreflex participates in short-term regulation of blood pressure, there is increasing evidence that baroreflexes do not completely reset with hypertension and may play a role in long-term cardiovascular control (Lohmeier and Iliescu 2015). Most notable among this evidence is the finding that chronic electrical activation of the carotid sinus in adult dogs results in sustained (3-week experimental period) decreases in blood pressure, whole-body norepinephrine turnover, and heart rate (Lohmeier et al. 2010). Unfortunately, no studies have addressed the role of the baroreflex in the long-term control of arterial pressure during development.

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## Cardiopulmonary Reflex

Cardiopulmonary receptors are sensory endings located in the four cardiac chambers, in the great veins, and in the lungs (Minisi and Thames 1991). In the adult, volume sensors mediating reflex changes in cardiovascular and renal function are believed to be primarily those residing in the atria (Goetz et al. 1991; Hainsworth 1991) and the ventricles (Minisi and Thames 1991), with the ventricular receptors being of utmost importance during decreases in cardiopulmonary pressures (Minisi and Thames 1991; Togashi et al. 1990; Victor et al. 1989). The majority of ventricular receptor vagal afferents are unmyelinated C fibers that can be activated by exposure to chemical irritants (chemosensitive) and changes in pressure or strength (mechanosensitive receptors) (Baker et al. 1979; Gupta and Thames 1983). These receptors have a low basal discharge rate which

exerts a tonic inhibitory influence on sympathetic outflow and vascular resistance (Minisi and Thames 1991) and regulates plasma AVP concentration (Thames et al. 1980). Interruption of this basal activity results in increases in heart rate, blood pressure, and sympathetic nerve activity, whereas activation of cardiopulmonary receptors results in reflex bradycardia, vasodilation, and sympathoinhibition (Minisi and Thames 1991).

Characterization of the cardiopulmonary reflex during the perinatal and neonatal periods by stimulation of chemosensitive cardiopulmonary receptors demonstrated that changes in heart rate, blood pressure, and regional blood flow were smaller early during development than later in life, and absent in premature fetal lambs and in piglets under 1-week-old (Assali et al. 1978; Gootman 1991; Gootman et al. 1986). Stimulation of cardiopulmonary receptors by volume expansion had no effect on basal renal nerve activity in the fetus but significantly reduced RSNA in newborn and 8-week-old sheep (Merrill et al. 1994; Smith et al. 1992). However, the decrease in RSNA in response to volume expansion was totally abolished in sinoaortic-denervated (SAD) newborn lambs but was not affected by SAD in 6–8-week-old sheep (Merrill et al. 1995). These results indicate that cardiopulmonary reflexes are not fully mature early in life and that stimulation of sinoaortic baroreceptors plays a greater role than cardiopulmonary mechanoreceptors in regulating changes in sympathetic activity in response to expansion of vascular volume early during development.

Developmental changes in cardiovascular and autonomic responses to blood volume reduction also exist. Gomez et al. found that hemorrhage produced a significant decrease in arterial blood pressure without accompanying changes in heart rate in fetal sheep less than 120-day gestation, whereas blood pressure remains stable and heart rate increased in near-term fetuses (Gomez et al. 1984). However, other investigators (Chen et al. 1992; Toubas et al. 1981) found the hemodynamic response to hemorrhage to be similar in immature and near-term fetuses, with reductions in both heart rate and blood pressure. Inhibition of vagal afferents during slow, non-hypotensive hemorrhage

blocks the normal rise in plasma vasopressin but does not alter the rise in plasma renin activity in near-term fetal sheep (Chen et al. 1992). When input from cardiopulmonary receptors is removed by section of the cervical vagosympathetic trunks, the decrease in fetal blood pressure in response to hemorrhage is similar to that in intact fetuses (Wood et al. 1989), whereas vagotomy with SAD enhances the decrease in blood pressure (Chen et al. 1992). Therefore, it is likely that activation of fibers from the carotid sinus (arterial baroreceptors and chemoreceptors) but not vagal afferents (cardiopulmonary baroreceptors and chemoreceptors) is involved in the maintenance of blood pressure homeostasis during fetal hemorrhage. Cardiopulmonary receptors also appear to have a diminished role in early postnatal life as reflex changes in newborn lamb RSNA during non-hypotensive and hypotensive hemorrhage are dependent upon the integrity of arterial baroreceptors but not cardiopulmonary receptors (O'Mara et al. 1995). In addition, the cardiovascular responses to hemorrhage in newborn lambs are dependent upon intact renal nerves that in turn modulate release of AVP (Smith and Abu-Amarah 1998).

The RSNA responses to vagal afferent nerve stimulation are similar in sinoaortic-denervated fetal and postnatal lambs, suggesting that delayed maturation of the cardiopulmonary reflex is not secondary to incomplete central integration of vagal afferent input (Merrill et al. 1999). On the other hand, the decreased sensitivity of the cardiopulmonary reflex early in development in the face of a sensitive arterial baroreflex response (as outlined above) may suggest that there is an occlusive interaction between these two reflexes during development. In support of this hypothesis, studies in adults suggest that activation of arterial baroreceptors may impair the reflex responses to activation of cardiopulmonary receptors (Cornish et al. 1989; Hajduczuk et al. 1991a).

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## Peripheral Chemoreflex

Peripheral chemoreceptors located in the aortic arch and carotid bodies are functional during fetal and postnatal life and participate in

cardiovascular regulation (Bishop et al. 1987; Cohn et al. 1974; Giussani et al. 1993). Acute hypoxemia evokes integrated cardiovascular, metabolic, and endocrine responses that in the fetus result in transient bradycardia, increased arterial blood pressure, and peripheral vascular resistance and a redistribution of blood flow (Cohn et al. 1974; Gardner et al. 2002). The bradycardia is mediated by parasympathetic efferents, as it can be blocked by atropine, while the peripheral vasoconstriction triggered by the chemoreceptor stimulation initially results from increased sympathetic tone and can be prevented with alpha-adrenergic antagonists (Giussani et al. 1993; Iwamota et al. 1983; Parer 1984). The release of circulating factors such as vasopressin (AVP) and catecholamines serves to maintain peripheral vasoconstriction while heart rate returns toward basal levels.

Oxygen sensing in the carotid body is transduced by glomus cells, specialized sensory neurons that respond to hypoxia at higher PaO<sub>2</sub> levels than other cell types. It is believed that in states of low O<sub>2</sub>, oxygen-sensitive K<sup>+</sup> currents are inhibited, resulting in depolarization, an influx of Ca<sup>2+</sup>, and the release of neurotransmitters and neuromodulators that generate an action potential in the carotid sinus nerve (Carroll and Kim 2005). Recordings from carotid chemoreceptors in fetal sheep demonstrated responses to natural stimuli from ca. 90 days of gestation (Blanco et al. 1984, 1988b). Fetal carotid chemoreceptors were active and responsive to hypoxia, but only to changes in PaO<sub>2</sub> within the fetal range. Furthermore, the position of the response curve of the chemoreceptors to hypoxia was shifted to the left, and the sensitivity to an absolute change of arterial PO<sub>2</sub> was less compared to that of the adult.

The ontogeny of fetal chemoreflex-mediated cardiovascular responses to acute hypoxemia has primarily been assessed by studies in sheep utilizing umbilical cord occlusion or administration of subambient oxygen to the ewe (Bennet et al. 1999; Giussani et al. 1993; Iwamota et al. 1983; Szymonowicz et al. 1990; Wassink et al. 2007). The cardiovascular response to acute fetal hypoxemia depends upon the prevailing intrauterine condition, including the redox state of the fetus

(Fletcher et al. 2006; Gardner et al. 2002; Hanson 1997; Herrera et al. 2012; Kane et al. 2012; Thakor and Giussani 2009a; Thakor et al. 2010). In fetal sheep, mild, acute acidemia ( $\text{pH } 7.29 \pm 0.01$ ), which often accompanies fetal hypoxemia, has no effects on basal cardiovascular function but markedly enhances peripheral vasoconstriction and endocrine responses to acute hypoxemia (Thakor and Giussani 2009a). To examine the effects of prevailing hypoxemia on responses to acute hypoxemia, Gardner et al. (2002) studied chronically instrumented fetal sheep grouped according to  $\text{PaO}_2$ . Functional chemoreflex analysis during early hypoxemia, performed by plotting the change in  $\text{PaO}_2$  against the change in heart rate and femoral vascular resistance, demonstrated that the slopes of the cardiac and vasoconstrictor chemoreflex curves were enhanced in hypoxemic fetuses relative to control. Additional evidence suggests exposure to hypoxemia for a limited period of time (hours to days) has a sensitizing effect on the chemoreflex, whereas sustained hypoxemia (days to weeks) may have a desensitization effect (Hanson 1997). The mechanisms regulating this alteration in response are unclear. In the chick embryo, hypoxia increases sympathetic nerve fiber density and neuronal capacity for norepinephrine synthesis (Ruijtenbeek et al. 2000). Thus, augmented efferent pathways may contribute to the enhanced responses. On the other hand, recordings from carotid chemoreceptors in chronically hypoxic kittens demonstrate blunted responses to acute decreases in  $\text{PaO}_2$  relative to control animals (Hanson et al. 1989). It is therefore possible that with prolonged hypoxia, blunting of the chemoreflex responses may be related to afferent mechanisms.

Although chemoreceptors are active and responsive in the fetus and newborn, studies in sheep and human infants suggest that chemoreceptor sensitivity and activity is reduced immediately after birth (Blanco et al. 1984; Hertzberg and Lagercrantz 1987). This decreased sensitivity persists for several days until the chemoreceptors adapt and reset their sensitivity from the low oxygen tension of the fetus to the higher levels seen postnatally (Hertzberg and Lagercrantz 1987; Kumar and Hanson 1989). The mechanisms

involved with this resetting are not known, although the postnatal rise in  $\text{PaO}_2$  appears crucial as raising fetal  $\text{PaO}_2$  produces a rightward shift in the response curve of carotid baroreceptors to differing oxygen tension (Blanco et al. 1988b). Potential mechanisms within the glomus cell regulating developmental changes in  $\text{O}_2$  transduction and chemoreceptor responses include, but are not limited to, anatomical maturation, developmental changes in oxygen-sensitive  $\text{K}^+$  currents, adenosine responsiveness (Koos et al. 1995; Koos and Maeda 2001), dopamine and catecholamine turnover within the carotid body (Hertzberg et al. 1992), and differences in intracellular calcium mobilization during hypoxia (Carroll and Kim 2005; Sterni et al. 1995).

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## Sympathetic Activity at Birth

The transition from fetal to newborn life is associated with numerous hemodynamic adjustments, including changes in heart rate and peripheral vascular resistance and a redistribution of blood flow (Dawes 1961; Padbury and Martinez 1988). Activation of the sympathetic nervous system appears to be an important part of this adaptive process and is associated with marked increases in circulating catecholamines (Lagercrantz and Bistoletti 1973; Padbury et al. 1981). Arterial pressure, heart rate, and cardiac output are all depressed by ganglionic blockade in newborn (1–3 days) but not older lambs, suggesting sympathetic tone is high during the immediate postnatal period (Minoura and Gilbert 1986). Renal sympathetic nerve activity increases nearly 250% following delivery of term fetal sheep by cesarean section and parallels the rise in arterial pressure and heart rate (Segar et al. 1994a). Delivery appears to produce near maximal stimulation of renal sympathetic outflow since further increases cannot be elicited by unloading of arterial baroreceptors (Segar et al. 1994a). Furthermore, reflex inhibition of this increase in RSNA could not be achieved by arterial baroreceptor stimulation, as seen in fetal and 3–7-day-old lambs (Segar et al. 1992), suggesting that central influences exist which override the arterial baroreflex and that

the maintenance of a high sympathetic tone is vital during this transition period. A similar pattern of baroreceptor gating has been well described in adult animals as part of the defense reaction (Hilton 1982). The cardiovascular component of this group of behavioral responses, characterized by sympathetic nerve-mediated tachycardia, increased cardiac contractile force, vasoconstriction, and hypertension, mimics the physiological changes that occur at birth (Gebber 1990).

The factors mediating the increase in sympathetic outflow at birth are unclear. Removal of the placental circulation, the onset of spontaneous respiration, and exposure to a cold environment are factors occurring at birth that may stimulate changes in sympathetic activity (Ogundipe et al. 1993; Van Bel et al. 1993). In utero ventilation studies of fetal sheep have shown that rhythmic lung inflation increases plasma catecholamine concentrations although there are no consistent effects on blood pressure or heart rate (Ogundipe et al. 1993; Smith et al. 1991). Fetal RSNA increases only 50% during in utero ventilation, while oxygenation and removal of the placental circulation by umbilical cord occlusion produce no additional effect, suggesting that lung inflation and an increase in arterial oxygen tension contribute little to the sympathoexcitation process (Mazursky et al. 1996). The increases in heart rate, mean arterial blood pressure, and RSNA following delivery are similar in intact and sinoaortic-denervated plus vagotomized fetal lambs, demonstrating that afferent input from peripheral chemoreceptors and mechanoreceptors also contribute little to the hemodynamic and sympathetic responses at delivery (Segar et al. 1999).

The change in environmental temperature at birth may play an important role in the sympathoexcitatory response at birth. Cooling of the near-term fetus both in utero and in exteriorized preparations results in an increase in heart rate, blood pressure, and norepinephrine concentrations, consistent with sympathoexcitation (Gunn et al. 1985; Van Bel et al. 1993). However, exteriorization of the near-term lamb fetus into a warm water bath does not produce the alterations in systemic

hemodynamics or catecholamine values typically seen at birth (Van Bel et al. 1993). Fetal cooling, but not ventilation or umbilical cord occlusion, initiates nonshivering thermogenesis via neurally mediated sympathetic stimulation of brown adipose tissue (Gunn et al. 1991). In utero cooling of fetal lambs also produces an increase in RSNA of similar magnitude to that seen at delivery by cesarean section (Waldman et al. 1979), suggesting that cold stress plays a role in the activation of the sympathetic nervous system at birth. These changes occur before a decrease in core temperature and are reversible with rewarming, suggesting that sensory input from cutaneous cold-sensitive thermoreceptors rather than a response to a change in core temperature is mediating the response. The increases in heart rate, mean arterial blood pressure, and RSNA that normally occur at birth are absent in animals subjected to transection of the brain stem at the level of the rostral pons prior to delivery (Mazursky et al. 1996). These data suggest that supramedullary structures are involved in mediating the sympathoexcitation seen at birth. Additional studies, also in fetal sheep, demonstrate the paraventricular nucleus of the hypothalamus plays a vital role in regulating postnatal increases in sympathetic outflow and baroreflex function (Ellsbury et al. 2000). Given the known role of the hypothalamus in temperature and cardiovascular regulation, this structure is likely intimately involved in the regulation of circulatory and autonomic functions during the transition from fetal to newborn life (Gebber 1990).

The hemodynamic and sympathetic responses at birth are markedly different in prematurely delivered lambs (0.85 of gestation) compared to those delivered at term (Segar et al. 1998). Postnatal increases in heart rate and blood pressure are attenuated, and the sympathoexcitatory response as measured by RSNA is absent (Segar et al. 1998). This impaired response occurs despite the fact the descending pathways of the sympathetic nervous system are intact and functional at this stage of development, as demonstrated by a large pressor and sympathoexcitatory response to in utero cooling (Segar et al. 1998). Antenatal administration of glucocorticoids, which has been shown to improve postnatal cardiovascular



as well as pulmonary function, augments sympathetic activity at birth in premature lambs and decreases the sensitivity of the cardiac baroreflex (Segar et al. 1998). Taken together, these data suggest exogenous glucocorticoids have a maturational effect on the sympathetic response at birth, which may be one mechanism by which maternal steroid administration improves postnatal cardiovascular homeostasis, though stimulation of the peripheral RAAS and activation of peripheral angiotensin receptors are not involved (Segar et al. 2001).

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**Humoral Factors (See Also  
► Chap. 2, “Vasoactive Factors  
and Blood Pressure in Children”)**

**Renin-Angiotensin-Aldosterone System**

The renin-angiotensin-aldosterone system (RAAS) is active in the fetal and perinatal periods (Guillery and Robillard 1993; Iwamoto and Rudolph 1979; Lumbers 1995). During embryonic and early fetal life, the primary function of the renin-angiotensin system may be to regulate cellular and organ growth as well as vascular proliferation (Kim and Iwao 2001). Only later during fetal development does the renin-angiotensin system become involved in modulating cardiovascular function and renal hemodynamics.

The arterial baroreflex not only modulates heart rate and peripheral vascular tone, the reflex also regulates the release of vasoactive hormones, such as ANG II and AVP (Wood 1995). Changes in the levels of these circulating hormones, in turn, may influence neural regulation of cardiovascular function by acting at several sites along the baroreflex arc (Bishop and Haywood 1991). In the adult, peripheral ANG II facilitates activation of sympathetic ganglia and enhances the release and response of norepinephrine at the neuro-effector junction (Reid 1992). Within the central nervous system, ANG II stimulates sympathetic outflow and alters baroreceptor reflexes by acting on ANG II type 1 (AT<sub>1</sub>) receptors located within the hypothalamus, medulla, and circumventricular

organs (Bunnemann et al. 1993; Head and Mayorov 2001; Toney and Porter 1993). In the sheep fetus, the increase in arterial blood pressure produced by ANG II administration produces little or no cardiac slowing (Jones III et al. 1991; Robillard et al. 1982), although dose-dependent decreases in heart rate may occur (Ismay et al. 1979; Scroop et al. 1986). The bradycardic and sympathoinhibitory responses to a given increase in blood pressure are less for ANG II than for other vasoconstrictor agents (Segar et al. 1994b).

Endogenous brain ANG II appears to contribute little to basal arterial pressure in fetal sheep though appears active postnatally. Lateral ventricle administration of an AT<sub>1</sub> receptor antagonist has no effect in the fetus but lowers blood pressure and resets the baroreflex toward lower pressure in newborn and 8-week-old sheep at doses that have no effect when given systemically (Segar et al. 1997). However, lateral ventricle injection of ANG II increases blood pressure in the fetus, an effect blocked by AT<sub>1</sub> receptor antagonists (Shi et al. 2005; Xu et al. 2003, 2004). Increased blood pressure via activation of angiotensin receptors was associated with elevated c-fos expression (a marker of neuronal activation) in numerous cardiovascular areas known to be AT<sub>1</sub> receptor abundant (Shi et al. 2005; Xu et al. 2003, 2004). An endogenous local RAAS in the brain, including ACE, also appears to be functional in the fetus, as intracerebroventricular injection of ANG I increases blood pressure and c-fos expression in the supraoptic nucleus and paraventricular nucleus (Shi et al. 2010).

Endogenous circulating ANG II participates in regulating arterial baroreflex responses early during development. The absence of rebound tachycardia after reduction in blood pressure by angiotensin-converting enzyme (ACE) inhibitors is well described in fetal and postnatal animals (Robillard et al. 1983) as well as in human adults and infants (Chatow et al. 1995). Converting enzyme inhibition has no effect on baroreflex control of RSNA in fetal sheep (Segar et al. 1994b). However, when enalapril is administered to the fetus immediately prior to delivery, baroreflex control of RSNA and heart rate in the newly born lamb is shifted toward lower pressures

(Segar et al. 1994a). Two- to fourfold higher levels of ANG II in the newborn than in fetal or adult sheep may help explain these observations (Robillard et al. 1982). Similarly, in the newborn lamb, angiotensin-converting enzyme inhibition or AT<sub>1</sub> receptor blockade decreases RSNA and heart rate and resets the baroreflex toward lower pressure (Segar et al. 1994b, 1997). Resetting of the reflex is independent of changes in prevailing blood pressure.

### Arginine Vasopressin

Several lines of evidence suggest that arginine vasopressin (AVP) is important in maintaining cardiovascular homeostasis during fetal and postnatal development. Fetal plasma AVP concentrations are increased by multiple stimuli, including hypotension, hemorrhage, hypoxemia, acidemia, and hyperosmolality (Robillard et al. 1979; Weitzman et al. 1978; Wood 1995; Wood and Chen 1989). Vasopressin responses to hypotension are partially mediated by arterial baroreceptors, whereas the contribution of carotid or aortic chemoreceptors appears to play little role in the AVP response to hypoxia (Giussani et al. 1994b; Raff et al. 1991). AVP infusion increases fetal blood pressure and decreases fetal heart rate in a dose-dependent manner (Irion et al. 1990; Tomita et al. 1985), although AVP has limited impact on basal fetal circulatory regulation. Blockade of AVP receptors in fetal sheep has no measurable effects on arterial blood pressure, heart rate, or renal sympathetic nerve activity in fetal sheep or newborn lambs (Ervin et al. 1992; Nuyt et al. 1996). However, AVP receptor inhibition impairs the ability of the fetus to maintain blood pressure during hypotensive hemorrhage and reduces the catecholamine response (Kelly et al. 1983).

In several adult species, AVP modulates parasympathetic and sympathetic tone and baroreflex function (Berecek and Swords 1990; Bishop and Haywood 1991; Luk et al. 1993; Nuyt et al. 1996). Administration of AVP evokes a greater sympathoinhibition and bradycardia than other vasoconstrictors for a comparable increase in blood pressure, this effect being attributed to

AVP enhancing the gain of the reflex and resetting it to a lower pressure (Bishop and Haywood 1991; Luk et al. 1993). However, in fetal and newborn sheep, sequential increases in plasma AVP do not alter heart rate or RSNA baroreflex responses to acute changes in blood pressure (Nuyt et al. 1996).

Endogenous AVP has little effect on baroreflex function early during development. Peripheral administration of a V<sub>1</sub> receptor antagonist has no measurable effects on resting hemodynamics in fetal sheep or on basal arterial blood pressure (Ervin et al. 1992), heart rate, RSNA, or baroreflex response in newborn lambs (Nuyt et al. 1996). This lack of baroreflex modulation by AVP may facilitate the pressor response to AVP in fetuses and newborns during stressful situations such as hypoxia and hemorrhage, which may be particularly important for maintaining arterial pressures during these states early in development.

The role of central AVP in maintaining hemodynamic homeostasis in the developing animal has not been extensively studied. Under basal conditions, fetal AVP levels are tenfold higher in the cerebrospinal fluid than in plasma, suggesting AVP contributes to central regulation of autonomic function (Stark et al. 1985). Intracerebroventricular infusion of AVP produces significant decreases in mean arterial blood pressure and heart rate in newborn lambs although no reflex changes in RSNA are seen (Segar et al. 1995). The changes in blood pressure and heart rate are completely inhibited by administration of an AVP receptor type 1 (V<sub>1</sub>) antagonist, demonstrating that central cardiovascular effects of AVP are mediated by V<sub>1</sub> receptors, as has been reported in mature animals (Unger et al. 1987).

### Glucocorticoids

The parturition surge in fetal cortisol levels that is present in all mammalian species is vital for normal physiological development. Fetal adrenalectomy attenuates the normal gestational age-dependent increase in blood pressure that occurs in late gestation, while cortisol replacement produces a sustained increase in fetal blood

pressure (Tangalakis et al. 1992; Unno et al. 1999). Antenatal exposure to exogenous glucocorticoids increases fetal and postnatal arterial blood pressure by enhancing peripheral vascular resistance and cardiac output without altering heart rate (Derks et al. 1997; Padbury et al. 1995; Stein et al. 1993). The use and effectiveness of hydrocortisone for hypotension in preterm and term neonates is well described (Ng et al. 2006; Seri et al. 2001). However, the mechanisms accounting for the increase in blood pressure and vascular resistance are not clear. In the adult, administration of hydrocortisone or dexamethasone suppresses resting and stimulated muscle sympathetic nerve activity, suggesting little role for augmented sympathetic tone (Dodt et al. 2000; Macefield et al. 1998). In contrast, glucocorticoids enhance pressor responsiveness and vascular reactivity to norepinephrine and angiotensin II (Grünfeld and Eloy 1987; Grünfeld 1990), in part by increasing  $\alpha$ 1-adrenergic and  $AT_1$  receptor levels and potentiating angiotensin II and vasopressin-induced inositol triphosphate production (Provencher et al. 1995; Sato et al. 1992). Glucocorticoids also reduce the activity of depressor systems, including vasodilator prostaglandins and nitric oxide, and have been shown to decrease serum  $NO_2^-/NO_3^-$ , endothelial nitric oxide synthase mRNA stability, and protein levels (Wallerath et al. 1999).

In the sheep fetus, cortisol infusion increases blood pressure as well as the hypertensive response to intravenous ANG II but not norepinephrine (Tangalakis et al. 1992). However, infusions of synthetic glucocorticoids, which also increase arterial blood pressure, do not alter the pressor response to phenylephrine, angiotensin II, or vasopressin (Fletcher et al. 2002). Furthermore, the increase in blood pressure is not inhibited by RAAS blockade (Segar et al. 2001). In vitro studies demonstrate that fetal treatment with betamethasone enhances the contractile response of femoral arteries to depolarizing potassium solutions, supporting a role for enhanced calcium channel activation (Anwar et al. 1999). Glucocorticoid exposure enhances in vitro responses of peripheral arteries to vasoconstrictors, including norepinephrine and endothelin 1, while attenuating vasodilator effects of forskolin and

bradykinin and nitric oxide production (Anwar et al. 1999; Docherty and Kalmar-Nagy 2001; Docherty et al. 2001; Molnar et al. 2002).

In addition to peripheral effects on vascular reactivity, antenatal glucocorticoids also modify autonomic and endocrine functions. Increases in fetal blood pressure and vascular resistance following betamethasone treatment occur despite marked suppression of circulating vasoconstrictors, including catecholamines, ANG II, and AVP (Derks et al. 1997; Ervin et al. 2000; Segar et al. 1998). Circulating neuropeptide Y concentration, which may provide an index of peripheral sympathetic activity, is increased following fetal exposure to dexamethasone (Fletcher et al. 2003). Glucocorticoid treatment accelerates postnatal maturation of brain catecholaminergic signaling pathways in rats and enhances renal sympathetic nerve activity in prematurely delivered lambs (Semenza 2000; Slotkin et al. 1992; Smith et al. 1992).

Endogenous production of cortisol is important for normal maturational changes in autonomic reflex function. Adrenalectomized sheep fail to display the normal postnatal increase in RSNA, while the response is restored by cortisol replacement (Segar et al. 2002). Restoring circulating cortisol levels to the prepartum physiological range shifts the fetal and immediate postnatal heart rate and RSNA baroreflex curves toward higher pressure without altering the slope of the curves (Segar et al. 2002). Antenatal administration of betamethasone decreases the sensitivity of baroreflex-mediated changes in heart rate in preterm fetuses and premature lambs (Segar et al. 1998) and alters baroreflex and chemoreflex function in fetal, newborn, and adult sheep (Ervin et al. 2000; Fletcher et al. 2002; Shaltout et al. 2010, 2011). Baroreflex control of heart rate and RSNA is reset upward in glucocorticoid-exposed animals, while baroreflex sensitivity is impaired, an effect that may be mediated through an imbalance of ANG II/angiotensin 1–7 (Shaltout et al. 2012). Sympathetic-mediated responses to behavioral or pharmacological challenges are also exaggerated in 6-week-old sheep following antenatal betamethasone exposure (Shaltout et al. 2011).

As with baroreflex function, there is evidence that fetal chemoreceptors are involved in modifying

the release of selective hormones in to the circulation, particularly glucocorticoids. Transection of the carotid sinus nerves in the sheep fetus delays the increase in plasma catecholamine concentrations during acute asphyxia (Jensen and Hanson 1995). Similarly, neural control of adrenocortical function is also evident in the late-gestation fetus as section of either the carotid sinus nerves or the splanchnic nerves affects the steroidogenic response without affecting the increase in ACTH during acute hypoxic or acute hypotensive stress (Giussani et al. 1994a; Myers et al. 1990; Riquelme et al. 1998). These studies suggest the presence of a carotid chemoreflex mediated by splanchnic nerve efferents that act to trigger the release of cortisol as well as sensitize the fetal adrenal cortex to ACTH delivery. Conversely, carotid sinus nerve section does not affect the release of AVP or of ANG II into the fetal circulation, suggesting these effects are not mediated by carotid chemoreceptors (Giussani et al. 1994b).

Glucocorticoid exposure also appears to alter the pattern and magnitude of fetal chemoreflex-mediated cardiovascular responses. Exposure of the preterm sheep fetus to synthetic glucocorticoids, such as dexamethasone, in doses of human clinical relevance results in more pronounced bradycardia and vasoconstriction in response to hypoxemia. Maternal intramuscular injection with dexamethasone or fetal intravenous infusion with dexamethasone at 0.7–0.8 of gestation switch the fetal bradycardic and femoral vasoconstrictor responses to acute hypoxia from the immature to the mature phenotype (Fletcher et al. 2003). With advancing gestation, and in close association with the parturition increase in fetal plasma cortisol, the magnitude and persistence of fetal bradycardia and vasoconstriction in response to hypoxemia become more pronounced (Fletcher et al. 2006).

## Nitric Oxide

Though not regarded as a classic neurohumoral factor, nitric oxide (NO) plays an important role in autonomic control of systemic hemodynamics early in development. NO synthase immunoreactivity has been demonstrated in multiple locations

along the central baroreflex pathway and preganglionic sympathetic neurons (Gai et al. 1995; Tanaka and Chiba 1994), which suggests that NO may function as a neurotransmitter to regulate arterial blood pressure in addition to its local regulation of vascular tone (Chlorakos et al. 1998; Sanhueza et al. 2005; Yu et al. 2002). In adult rats, NO within the paraventricular nucleus may exert a sympathoinhibitory effect (Rossi et al. 2010). Downregulation of neuronal NO synthase in the NTS reduces baroreflex tachycardic responses to acute hypotension but not reflex bradycardia to acutely increased blood pressure (Lin et al. 2012). Thus, NO synthesized in the NTS may be integral to baroreflex sympathetic activation, but not parasympathetic responses. Using a nitric oxide clamp technique, Thakor et al. demonstrated in fetal sheep that NO synthase blockade increases the sensitivity of the baroreflex, suggesting that endogenous NO reduces baroreflex sensitivity (Thakor and Giussani 2009b). Administration of the NO donor nitroglycerin into the fourth cerebral ventricle of the ovine fetus decreases mean arterial pressure, whereas blocking NO synthase in the fourth ventricle increases fetal blood pressure (Ma et al. 2003). Expression of NO synthase isoforms in the fetal sheep brain stem is highest early in gestation and decreases with advancing age (Wood et al. 2005). Reduced expression of NO synthase in these regions may contribute to the reduced baroreflex sensitivity of the fetus early in life. In 1- and 6-week-old lambs, inhibition of endogenously produced NO increases blood pressure to similar extents although the concomitant decreases in heart rate are greater in the young lamb (McDonald et al. 2000). Endogenous nitric oxide also appears to regulate arterial baroreflex control of heart rate in 1-week but not 6-week-old lambs, again supporting a possible role in the developmental changes in baroreflex function during this period (McDonald et al. 2000).

## Reactive Oxygen Species

Reactive oxygen species (ROS) signaling has emerged as a major mechanism of sympathetic activation. Under normotensive conditions, brainstem

ROS has a general excitatory effects on sympathetic outflow and cardiac baroreflex. Injection of superoxide dismutase into RVLM of young pigs resulted in moderate decreases in mean arterial blood pressure, heart rate, and RSNA (Zanzinger and Czachurski 2000). Increased oxidative stress, resulting from an imbalance between reactive oxygen species production and degradation in the rostral ventrolateral medulla, contributes to hypertension by enhancing central sympathetic outflow (Hirooka 2011). Oxidative stress also appears to be a key mechanism in ANG II-dependent neurogenic hypertension (Braga et al. 2011). In humans and animal models, chronic intermittent hypoxia, as occurs with recurrent apnea, increases ROS generation through transcriptional dysregulation of genes encoding pro- and antioxidant enzymes (Prabhakar et al. 2012). In juvenile rats (19–21 days of age), chronic intermittent hypoxia for 10 days results in significantly increased blood pressure and sympathetic overactivity, though cardiac baroreflex function remains intact (Zoccal et al. 2008, 2009). In a series of studies, Giussani and colleagues identified important roles of reactive oxygen species and nitric oxide bioavailability in modulating cardiovascular defense responses to acute hypoxia in fetal sheep (Herrera et al. 2012; Kane et al. 2012; Thakor et al. 2010). Whether these effects are mediated through mechanism similar to those described in the adult is not known.

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## Autonomic Function During Human Development

In human neonates and children, autonomic function has most simplistically been studied by examining changes in heart rate, various indices of heart rate variability, and blood pressure in response to postural changes which unload (head-up position) or load (head-down position) arterial baroreceptors. Some investigators have been unable to demonstrate a consistent response of heart rate during the neonatal period to tilting and concluded that the heart rate component of the baroreflex is poorly developed early in life, while others have demonstrated in healthy preterm and term infants that unloading arterial baroreceptor

by head-up tilting produces a significant heart rate response (Picton-Warlow and Mayer 1970; Thoresen et al. 1991; Waldman et al. 1979). Using venous occlusion plethysmography, Waldman et al. (1979) found in healthy preterm and term infants that 45° head-up tilting produced no significant tachycardia, although a mean 25% decrease in limb blood flow was observed, suggesting increased peripheral vascular resistance. In contrast, Meyers et al. found that 1–2-day-old healthy, term newborns display changes in heart rate with head-up and head-down tilt similar to those observed in the adult (Myers et al. 2006). Interestingly, at 2–4 months of age, the increase in heart rate to unloading of baroreceptors (head-up tilt) is lost (Fifer et al. 1999; Myers et al. 2006). The change in heart rate parasympathetic cardiac response to standing increased in children 6–19 years of age (Yamanaka and Honma 2006; Zhao et al. 2015).

Linear heart rate variability analysis in both the time and frequency domains, which quantifies the small spontaneous beat-by-beat variations in heart rate, has been used in human infants (Andriessen et al. 2005; Chatow et al. 1995; Clairambault et al. 1992) and fetuses (David et al. 2007; Karin et al. 1993; Schneider et al. 2009) to evaluate the contribution of the autonomic nervous system in maintaining cardiovascular homeostasis. An increase in sympathetic tone appears around 0.8 of gestation, followed by moderation of sympathetic outflow related to the establishment of fetal behavioral states (David et al. 2007). In the newborn, there is a progressive decline in the ratio of the low-frequency (LF) to high-frequency (HF) components of the heart rate power spectrum with increasing postnatal and gestational age, indicating an increase in parasympathetic contribution to control of resting HR with maturation. Clairambault et al. found that changes in the HF component of the spectrum were greater at 37–38 weeks, suggesting a steep increase in vagal tone at this age (Clairambault et al. 1992). Power spectral analysis has also been used to characterize developmental changes in sympathovagal balance in response to arterial baroreceptor unloading in preterm infants beginning at 28–30-week post-conceptual age (Mazursky et al. 1998).

Longitudinal examination of heart rate power spectra found that in infants at 28–30 weeks, the LF/HF ratio did not change with head-up postural change, whereas with increasing postnatal age, the LF component of the spectrum increases with head-up tilt (Mazursky et al. 1998). In an elegant cross-sectional study of 1-week-old infants with postmenstrual ages 28–42 weeks, Andriessen found increases in R-R interval, low- and high-frequency spectral powers, and baroreflex sensitivity with postmenstrual age (Andriessen et al. 2005). Taken together, these findings suggest that neural regulation of cardiac function, particularly parasympathetic modulation, undergoes maturational change and becomes more functional with postnatal development.

More recently, the use of noninvasive blood pressure techniques, primarily plethysmography, has further advanced our understanding of autonomic functional changes with maturation. Using this technique to examine sequences of spontaneous changes in blood pressure and heart rate in infants 24-week gestational age to term, Gournay et al. reported baroreflex sensitivity increased with gestational age and in premature infants <32-week gestation with postnatal age (Gournay et al. 2002). In contrast, Witcombe et al. found that preterm infants, but not term infants, when first studied at 2–4-week corrected age, had no maturational increase in spontaneous baroreflex sensitivity over the next 6 months of life (Witcombe et al. 2012). Differential rates of maturation in preterm and term infants of parasympathetic contributions to heart rate, which falls in the first month of life, followed by progressive increases between 1- and 6-month postnatal age, may contribute to these findings. In term infants studied over the first 6 months of life, Yiallourou et al. found that spontaneous baroreflex sensitivity was decreased in prone compared to supine infants at 2–3 and 5–6 months of age, parasympathetic control of heart rate strengthened with postnatal age while sympathetic vascular modulation decreased (Yiallourou et al. 2011, 2012). Preterm infants showed similar maturational changes in parasympathetic and sympathetic modulation of end-organ responses, though even when corrected for postmenstrual age, preterm infants displayed

reduced parasympathetic and sympathetic modulation of heart rate and blood pressure, respectively (Yiallourou et al. 2013).

Extending beyond the newborn period, longitudinal study of children during the first 5 years of life suggested increasing parasympathetic and decreasing sympathetic tone both contribute to the maturational decrease in heart rate (Alkon et al. 2011). Cross-sectional study of healthy subjects 7–22 years of age revealed cardiovascular baroreflex sensitivity markedly increase and peak at adolescence (15–18 years of age) (Lenard et al. 2004). In contrast, Zavodna et al. found no age-related changes in 11–22-year-olds, while Chirico et al. found baroreflex sensitivity to decrease with maturation from early to post-puberty in males, but not females (Chirico et al. 2015; Zavodna et al. 2006). Differences in findings may be related to methodology, physical activity patterns of study subjects, and other genetic and environmental factors (Tanaka et al. 1994).

In adults, initial stages of hypertension are associated with elevated sympathetic drive and baroreflex impairment. Autonomic dysregulation may be primary (causative) or secondary effects for the development of hypertension. Studies of the contribution of these factors in children are limited. In a small group of adolescence, fast Fourier analysis of heart rate variability showed a trend toward sympathetic predominance during reactivity testing those with higher diastolic blood pressure levels (Urbina et al. 1998). In a study of 10-year-old children, Genovesi et al. found spontaneous baroreflex impairment and reduced R-R interval variability (suggestive of dysfunctional vagal regulation of SA node) in prehypertensive (90–95th percentile for age, gender, and height) and hypertensive subjects (>95th percentile) compared to controls (Genovesi et al. 2008). Eleven- to fourteen-year-olds with blood pressure > 95th percentile after adjustment of age, sex, and height displayed elevated LF/HF blood pressure variability, suggestive of increased sympathetic activity and decreased cardiac baroreflex sensitivity compared to those with normal blood pressure (Fitzgibbon et al. 2012). These data suggest that early autonomic dysfunction, including

baroreflex impairment, could contribute to the later development of hypertension in a subset of children.

In addition to physical maturation, weight status influences autonomic function in the pediatric population. In a review of 20 studies examining the effects of weight on heart rate variability, Eyre et al. found a majority of studies reported that parasympathetic activity to the heart is reduced in obese children with a relative increase in cardiac sympathetic activity (Eyre et al. 2014). Impairment of baroreflex sensitivity in obese children closely correlates with the degree of insulin resistance (Cozzolino et al. 2015). Autonomic impairment is present in overweight children in spite of heavy physical activity (Lucini et al. 2013). However, weight reduction induces a change in autonomic activity toward parasympathetic dominance and an increase in heart rate variability (Mazurak et al. 2016).

## Conclusion

Understanding the mechanisms regulating cardiovascular function in the perinatal and postnatal periods is important. Failure to regulate arterial pressure, peripheral resistance, and organ blood flow may lead to significant variations in substrate delivery, resulting in ischemic or hemorrhagic injury. Autonomic regulatory mechanisms, including baroreceptors and chemoreceptors, are major modulators of blood pressure and circulatory function throughout life. Humoral and endocrine factors, including many not addressed, such as opioids, natriuretic peptides, and prostanoids, also act directly and indirectly to regulate vascular tone and cardiac function. Additional study is needed to determine the role of these factors, maturation, lifestyle choices, and their respective interactions on long-term cardiovascular health.

## Cross-References

- [Vasoactive Factors and Blood Pressure in Children](#)

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# Vasoactive Factors and Blood Pressure in Children

# 2

Ihor V. Yosypiv

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## Abstract

Control of arterial blood pressure (BP) is accomplished, in part, by the net effect of vasodilator and vasoconstrictor substances. This chapter presents current data on the ontogeny of the most relevant vasoactive peptide systems in the systemic circulation and in the developing kidney, and highlights how any alteration in the integrity of vasomotor control may lead to deregulation of BP and associated hypertension in children.

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## Keywords

Renin • Angiotensin II • ACE • Kallikrein • Nitric oxide • Endothelin • Urotensin 1

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## Introduction

Vasoactive peptide systems play a critical role in the regulation of arterial blood pressure (BP). Inappropriate stimulation or deregulation of physiological cross-talk among diverse vasomotor factors often contributes to or accounts for the development of hypertension, cardiovascular, and kidney disease in children. Understanding how derangements in vasoactive factor systems lead to such health problems might potentially prevent future disease. This chapter reviews newer advances in physiology, biochemistry, and

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pathophysiology, and function of the renal and systemic vasoactive systems with special emphasis on their role in the pathogenesis of hypertension in children.

### The Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system (RAAS) plays a fundamental role in the regulation of arterial BP. Emerging evidence suggests that local tissue-specific formation of components of the RAAS is of major importance in the regulation of the angiotensin (Ang) levels in many organs (Navar et al. 2002, Kobori et al. 2006). The components of the RAAS are shown in Fig. 1. Renin cleaves its substrate, angiotensinogen (AGT), to generate Ang I [Ang-(1-10)] (Fig. 1). Ang I is then converted to Ang II [Ang-(1-8)] by angiotensin-converting enzyme (ACE). ACE expression on endothelial cells of many vascular beds including the kidney, heart, and lung allows systemic formation of Ang II, the most powerful effector peptide hormone of the RAAS, active throughout the circulation and locally, within tissues (Brasier and Li 1996; Navar 1997; Paul et al. 2006). Most of hypertensinogenic actions of Ang II are attributed to the AT<sub>1</sub> receptor

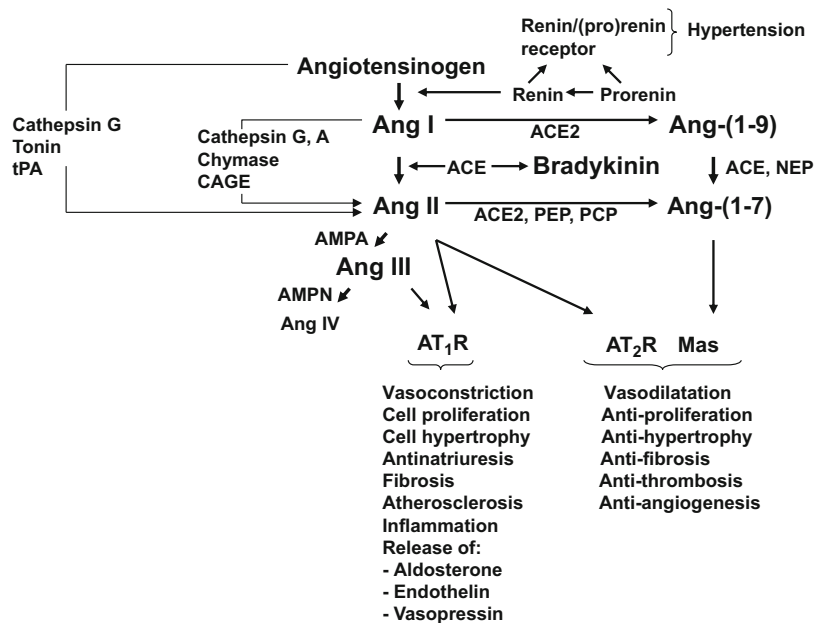
(AT<sub>1</sub>R) (Ito et al. 1995). Binding of prorenin to the (pro)renin receptor induces a conformational change of prorenin, facilitating the conversion of AGT to Ang I (Nguyen et al. 2002). ACE2, a homolog of ACE, acts to promote Ang II degradation to the vasodilator peptide Ang-(1-7) (Donoghue et al. 2000; Brosnihan et al. 1996). Ang-(1-7) acts via its cognate receptor, Mas, to counteract Ang II-AT<sub>1</sub>R-mediated effects (Santos et al. 2003; Santos and Ferreira 2007).

### Angiotensinogen

Angiotensinogen (AGT) is formed and constitutively secreted into the circulation by the hepatocytes (Fukamizu et al. 1990). In addition, AGT mRNA and protein are expressed in kidney proximal tubules, central nervous system, heart, adrenal gland, and other tissues (Ingelfinger et al. 1990; Lynch and Peach 1991). Although AGT is the only substrate for renin, other enzymes can cleave AGT to form Ang I or Ang II (Fig. 1) (Yosipiv and El-Dahr 1996; Miyazaki and Takai 2001). Expression of the *AGT* gene is induced by Ang II, glucocorticoids, estrogens, thyroxine, and sodium depletion (Lynch and Peach 1991; Schunkert et al. 1992; Kobori et al. 2007).

**Fig. 1** The renin-angiotensin-aldosterone system.

The renin-angiotensin-aldosterone system is shown in this figure. Abbreviations: Ang, angiotensin (I, II or III); CAGE, chymostatin-sensitive Ang II-generating enzyme, AMPN aminopeptidase N, tPA tissue plasminogen activator



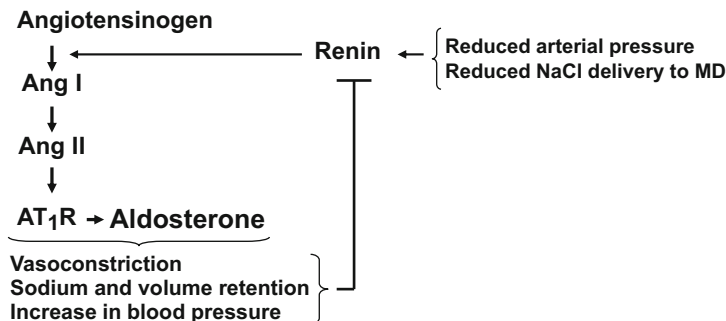
Importantly, A/G polymorphism at  $-217$  in the promoter of the *AGT* gene appears to play an important role in hypertension in African-Americans (Jain et al. 2002). A significant association of a T704→C (Met235→Thr) variant in exon 2 of the *AGT* gene with essential hypertension was reported in the cross-sectional study in Salt Lake City and Paris (Jeunemaitre et al. 1992). Recent meta-analysis indicated significant association between A-6G and A-20C polymorphisms in the *AGT* promoter and hypertension in the Chinese populations (Gu et al. 2011).

### Prorenin, Renin, and (Pro)renin Receptor

Renin is synthesized as preprorenin in juxtaglomerular cells of the afferent arterioles of the kidney (Hackenthal et al. 1990). The human renin gene encoding preprorenin is located on chromosome 1 (Miyazaki et al. 1984). Cleavage of a 23 amino acid signal peptide at carboxyl terminus of preprorenin generates prorenin which is then converted to active renin by cleavage of 43-amino acid N-terminal prosegment by proteases (Paul et al. 2006; Schweda et al. 2007). The kidney secretes both renin and prorenin into the peripheral circulation. Plasma levels of prorenin are approximately tenfold higher than those of renin (Danser et al. 1998). Renin release is

controlled by baroreceptors in the afferent arterioles of the glomeruli, chloride-sensitive receptors in the macula densa (MD) and juxtaglomerular apparatus, and renal sympathetic nerve activity in response to changes in posture or effective circulating fluid volume (Fig. 2) (Lorenz et al. 1993; Davis and Freeman 1976; Burns et al. 1993; Handa and Johns 1985). Inhibition of renin secretion in response to an increase in NaCl at the MD is adenosine-dependent, whereas stimulation of renin release by a low perfusion pressure depends on cyclooxygenase-2 and neuronal nitric oxide (NO) synthase (NOS) (Kim et al. 2006; Zhou et al. 2004; Touyz and Schiffrin 2000). In contrast, changes in AGT synthesis occur more slowly and thus are less responsible for the dynamic regulation of plasma Ang I and Ang II than renin (Brasier and Li 1996; Deschepper 1994). In addition, the circulating concentrations of AGT are more than 1000 times greater than the plasma Ang I and Ang II levels (Navar et al. 2002). Therefore, renin activity is the rate-limiting factor in Ang I formation from AGT (Paul et al. 2006). Although Ang II can be generated from AGT or Ang I via renin/ACE-independent pathways (Yosipiv and El-Dahr 1996; Miyazaki and Takai 2001), the circulating levels of Ang II primarily reflect the consequences of renin action on AGT (Erdös and Skidgel 1990).

The renin/prorenin-(pro)renin receptor complex has emerged as a newly discovered pathway for



**Fig. 2** The renin-angiotensin-aldosterone system in vasoconstriction and renal sodium and water retention. Renin-angiotensin-aldosterone system is shown in vasoconstriction, renal sodium, and water retention. Renin is secreted in response to reduced arterial pressure or NaCl delivery to macula densa (MD) and cleaves angiotensinogen

to Ang I. Ang I is converted to Ang II by ACE. Ang II acts via the AT<sub>1</sub> receptor (AT<sub>1</sub>R) to increase blood pressure by arteriolar vasoconstriction and stimulate aldosterone secretion. Ang II and aldosterone also cause renal sodium and water retention leading to suppression of renin release

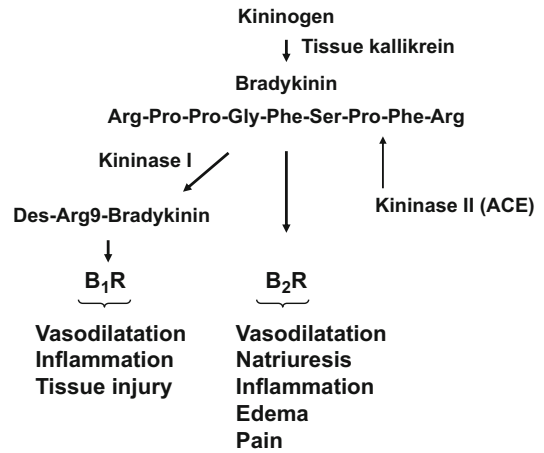
tissue Ang II generation. In addition to proteolytic activation, prorenin may be activated by binding to (pro)renin receptor (PRR) (Nguyen et al. 2002).

The (pro)renin receptor (PRR) is expressed on mesangial and vascular smooth muscle cells and binds both prorenin and renin (Batenburg et al. 2007). Binding of renin or prorenin to the PRR induces a conformational change of prorenin facilitating catalytic activity and the conversion of AGT to Ang I (Nguyen et al. 2002). A direct pathological role of the PRR in hypertension is suggested by the findings of elevated BP in transgenic rats that overexpress the human PRR (Burcklé et al. 2006). An important role for the PRR in the pathogenesis of hypertension in humans is supported by the findings that a polymorphism in the *PRR* gene is associated with a high BP in men (IVS5 + 169C > T) and left ventricular hypertrophy in women (+1513A > G) (Hirose et al. 2009, 2011; Ott et al. 2011). Two single-nucleotide polymorphisms in the *PRR* gene (rs296815; rs5981008) were reported to be significantly associated with hypertension in adult Caucasians (Brugts et al. 2011).

## Angiotensin-Converting Enzyme

Angiotensin-converting enzyme (ACE) is involved in the posttranslational processing of many polypeptides, the most notable of which are Ang I and bradykinin (BK) (Figs. 1 and 3). There are two ACE isozymes, somatic and testicular, transcribed from a single gene by differential utilization of two distinct promoters (Kumar et al. 1991). Human somatic ACE contains 1306 amino acids and has a molecular weight of 140–160 kilodaltons (kDa). In the kidney, ACE is present as an ectoenzyme in glomerular vascular endothelial and proximal tubular cells (Ramchandran et al. 1994). ACE localized in glomerular endothelium may regulate intraglomerular blood flow, whereas ACE expressed in the proximal tubular epithelia and postglomerular vascular endothelium may play an important role in the regulation of tubular function and postglomerular circulation.

An important role for ACE in normal kidney development and the regulation of BP is evident



**Fig. 3** The kallikrein-kinin system. This depicts the kallikrein-kinin system

from the findings that *ACE* mutations are linked to an autosomal recessive renal tubular dysgenesis (RTD), a severe disorder of renal tubular development characterized by persistent fetal anuria, pulmonary hypoplasia, and refractory arterial hypotension (Gribouval et al. 2005). The human *ACE* gene contains a polymorphism consisting of either an insertion (I) or deletion (D) of a 287 bp Alu repetitive sequence in intron 16. It has been demonstrated that allelic *ACE* variation is responsible for 47% of the variance of plasma ACE activity (Rigat et al. 1990). Notably, D allele and the DD genotype have been reported to be associated with elevated levels of ACE and a higher risk of left ventricular hypertrophy and hypertension in humans (Higaki et al. 2000; Iwai et al. 1994). In addition, ACE enzymatic activity, ACE D allele frequency and systolic BP were higher in low birth weight (LBW) compared with normal birth weight children (Ajala et al. 2012). Thus, ACE DD genotype can be an important factor in association between LBW and high BP levels.

## Angiotensin II Receptors

Ang II acts via two major types of G protein-coupled receptors (GPCR): AT<sub>1</sub>R and AT<sub>2</sub>R. In rodents, AT<sub>1</sub>R has two distinct subtypes, AT<sub>1A</sub> and AT<sub>1B</sub>, with greater than 95% amino acid sequence homology (Iwai and Inagami 1992).

In the kidney, AT<sub>1</sub>R mRNA has been localized to proximal tubules, the thick ascending limb of the loop of Henle, glomeruli, arterial vasculature, vasa recta, arcuate arteries, and juxtaglomerular cells (Tufro-McReddie and Gomez 1993). Activation of the AT<sub>1</sub>R increases BP in three ways. First, via direct vasoconstriction and increase in peripheral vascular resistance; second, by stimulation of Na<sup>+</sup> reabsorption via NHE3 at the proximal nephron and by NHE3 and bumetanide-sensitive cotransporter 1 (BSC-1) at the medullary thick ascending limb of the loop of Henle; and third, via stimulation of aldosterone biosynthesis and secretion by the adrenal zona glomerulosa (Fig. 2) (Holland et al. 1995; Morganti et al. 1979; Goodfriend et al. 1996). AT<sub>1</sub>R activation also stimulates vasopressin and endothelin secretion, the sympathetic nervous system, and proliferation of vascular smooth muscle and mesangial cells (Gasparo et al. 2000; Berry et al. 2001; Wolf et al. 1992). The AT<sub>2</sub>R has 34% homology with AT<sub>1A</sub> or AT<sub>1B</sub> receptors (Inagami et al. 1993). AT<sub>2</sub>R is expressed in the glomerular epithelial cells, proximal tubules, collecting ducts, and parts of the renal vasculature of the adult rat (Miyata et al. 1998). In contrast to AT<sub>1</sub>R, AT<sub>2</sub>R elicits vasodilation by increasing the production of nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) either by stimulating formation of bradykinin or by direct activation of NO production (Siragy and Carey 1997; Tsutsumi et al. 1999; Abadir et al. 2003). In addition, the AT<sub>2</sub>R promotes renal sodium excretion and inhibits proliferation in mesangial cells (Siragy and Carey 1997; Goto et al. 1997; Gross et al. 2000). Thus, the AT<sub>2</sub>R might oppose AT<sub>1</sub>R-mediated effects on blood pressure, cardiovascular and renal growth, fibrosis, and remodeling, as well as RBF, fibrosis, and sodium excretion.

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## Angiotensin-Converting Enzyme 2

Angiotensin-converting enzyme 2 (ACE2), a homolog of ACE, is abundantly expressed in the kidney and acts to counterbalance ACE activity by promoting Ang II degradation to the vasodilator peptide Ang-(1-7) (Donoghue et al. 2000;

Brosnihan et al. 1996). Ang-(1-7) acts via the GPCR Mas encoded by the *Mas* protooncogene and counteracts Ang II-AT<sub>1</sub>R-mediated effects (Santos et al. 2003; Santos and Ferreira 2007). An important role for ACE2 in the regulation of BP is suggested by the findings of a decreased ACE2 expression in the kidney of hypertensive rats and a reduction of BP following genetic overexpression of ACE2 in their vasculature (Zhong et al. 2004; Rentzsch et al. 2008). Although ACE2-null mice are normotensive and have normal cardiac structure and function, they exhibit enhanced susceptibility to Ang II-induced hypertension (Gurley et al. 2006). Studies in mice have demonstrated that, during Ang II infusion, administration of recombinant ACE2 (rACE2) results in Ang II degradation and a decrease in BP (Wysocki et al. 2010). The mechanism of rACE2 action results from an increase in systemic, not kidney or cardiac tissue, ACE2 activity and from the lowering of plasma Ang II rather than the attendant increase in Ang-(1-7). Thus, increasing ACE2 activity may provide a new therapeutic target in states of Ang II overactivity. Moreover, *Mas*-deficient mice exhibit increased BP, endothelial dysfunction, and an imbalance between NO and reactive oxygen species (Xu et al. 2008). Other major degradation products of Ang II include Ang III [Ang-(2-8)] and Ang IV [Ang-(3-8)]. These peptides have biological activity, but their plasma levels are much lower than those of Ang II or Ang-(1-7) (Haulica et al. 2005).

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## Developmental Aspects of the RAAS

The developing metanephric kidney expresses all the components of the RAAS (Table 1). The activity of the renal RAAS is high during fetal and neonatal life and declines postnatally (Gomez et al. 1989; Yosipiv and El-Dahr 1995). Immunoreactive Ang II levels are higher in the fetal and newborn kidney than in the adult rat kidney (Yosipiv and El-Dahr 1995). The ontogeny of AT<sub>1</sub>R and AT<sub>2</sub>R mRNA in the kidney differs. AT<sub>2</sub>R mRNA is expressed earlier than AT<sub>1</sub>R, peaks during fetal metanephrogenesis and rapidly declines postnatally (Norwood et al. 1997;

**Table 1** Expression of the renin-angiotensin-aldosterone system components during metanephric kidney development

	E12	E14	E15	E16	E19	References
<b>AGT</b>						
<i>Mouse:</i>	UB, SM	UB, SM, PT				Cheung (1995)
			<i>Rat:</i> UB, SM	UB, SM, PT	PT	Norwood et al. (1997)
<b>Renin</b>						
<i>Mouse:</i>	precursor cells present M of entire kidney M, close to V and G, V, G					Oliverio et al. (1998)
			<i>Rat:</i> V	V	V	Esther et al. (1996)
<b>ACE</b>						
				<i>Rat:</i> PT, G, CD		Hackenthal et al. (1990)
<b>ACE2</b>						
<i>Mouse</i>		UB, G, PT		PT		Yu et al. (2002)
<b>AT<sub>1</sub></b>						
<i>Mouse:</i>	UB, M	UB, G	UB, V	PT, UB, SM, G	PT, DT	Cheung (1995), Iosipiv and Schroeder (2003)
						Inagami et al. (1993)
			<i>Rat:</i> G, UB, SM	SM	PT, CD, G	Kielstein et al. (2004), Prieto et al. (2001)
<b>AT<sub>2</sub></b>						
<i>Mouse:</i>	MM	MM, SM	Medullary SM, under renal capsule			Inagami et al. (1993)
		<i>Rat:</i> MM	Condensed M	Medulla, G, V		Kielstein et al. (2004)
<b>PRR</b>	<i>Mouse:</i> UB	UB, CM	UB	T, G	T,G	Zhang et al. (2007)

*AGT* angiotensinogen, *ACE* angiotensin-converting enzyme, *ACE<sub>2</sub>* angiotensin-converting enzyme 2, *AT<sub>1</sub>/AT<sub>2</sub>* angiotensin II receptors, *UB* ureteric bud, *M* mesenchyme, *SM* stromal mesenchyme, *PT* proximal tubule, *DT* distal tubule, *G* glomeruli, *V* renal vessels, *CD* collecting duct, *PRR* (pro)renin receptor

Garcia-Villalba et al. 2003). *AT<sub>1</sub>R* mRNA expression increases during gestation, peaks perinatally and declines gradually thereafter (Norwood et al. 1997; Kakuchi et al. 1995). *ACE* mRNA and enzymatic activity are expressed in the developing rat kidney, where they are subject to regulation by endogenous Ang II and bradykinin (Yosipiv et al. 1994; Kakuchi et al. 1995). In addition, the developing kidney expresses considerable *ACE*-independent Ang II generating activity (Yosipiv and El-Dahr 1995, 1996), which may compensate for the low *ACE* levels in the early metanephros (Yosipiv et al. 1994). *ACE2* mRNA and protein are expressed in the developing mouse kidney as early as on E12.5 (Song et al. 2012). Ang II, acting via the *AT<sub>1</sub>R*, exerts a negative feedback on *ACE2* in the developing metanephros. In the

mouse kidney, (pro)renin receptor mRNA (*PRR* mRNA) is expressed in the intact ureteric buds (*UBs*) isolated from embryonic (E) day E11.5 wild-type mouse kidneys (Song et al. 2013a). In the whole metanephros, *PRR* mRNA and protein are detected from E12.5 while *PRR* immunostaining is present in the *UB*, a precursor of the renal collecting system and the cap mesenchyme, which contains nephron progenitors, on E13.5 (Table 1). Kidney *PRR* protein levels are high throughout gestation and decline gradually during postnatal development. On E16.5 and E18.5, *PRR* immunostaining is most prominent in the tubules which resemble morphologically collecting ducts followed by glomerular mesangium (Song et al. 2013b). To circumvent the early lethality of the global *PRR* knockout in mice and to drive deletion

of *PRR* in specific lineages of the developing kidney, recent studies used a Cre-lox conditional targeting approach and demonstrated that *PRR* is critical for normal kidney development and function. *PRR* deletion in mice podocytes using the *Nphs2* promoter results in massive foot process effacement, proteinuria, and nephrotic syndrome (Oshima et al. 2011; Riediger et al. 2011). *PRR* ablation in the UB epithelia using the *Hoxb7* promoter leads to kidney hypoplasia, reduced kidney function, polyuria, and a reduced capacity to acidify the urine (Song et al. 2013a). Inactivation of the *PRR* in nephron progenitors results in small cystic kidneys at birth, reduced nephron endowment, resulting in later glomerular kidney disease with focal glomerulosclerosis, proteinuria, and decreased kidney function (Song et al. 2016).

The role of the ACE2-Ang-(1-7)-Mas axis and the *PRR* in developmental origins of hypertension remains to be determined. Functionally, Ang II, acting via the AT<sub>1</sub>R, counteracts the vasodilator actions of bradykinin on the renal microvasculature of the developing rat kidney (El-Dahr et al. 1995). Premature infants exhibit markedly elevated PRA, which is inversely related to post-conceptual age (Richer et al. 1977). In healthy children, plasma renin activity (PRA) is high during the newborn period and declines gradually towards adulthood (Stalker et al. 1976).

Pharmacologic or genetic interruption of the RAAS during development alters BP phenotype and causes a spectrum of congenital abnormalities of the kidney and urinary tract (CAKUT) in rodents and RTD, renal failure, and other abnormalities (e.g., hypocalvaria) in humans (Table 2) (Gribouval et al. 2005; Sánchez et al. 2008). Therefore, RAAS inhibitors should not be used during pregnancy and postnatally until nephrogenesis is completed. Beyond these periods of life, high activity of the RAAS coupled with persistent expression of the renal AT<sub>1</sub>R provide the foundation for the use of the classical RAAS inhibitors (ACE inhibitors and AT<sub>1</sub>R antagonists) in the treatment of children with RAAS-dependent hypertension (e.g., renovascular hypertension). In addition, RAAS inhibitors may be beneficial in children with primary hypertension and

particularly in obese adolescents, who exhibit elevated plasma renin activity (Flynn 2011). Recent availability of a direct inhibitor of (pro)renin receptor offers new possibilities in antihypertensive therapy in children that remain to be explored (Flynn and Alderman 2005).

## Aldosterone

Ang II, acting via the AT<sub>1</sub>R, stimulates an increase in transcription and expression of the rate-limiting enzyme in the biosynthesis of aldosterone, CYP 11B2 (aldosterone synthase) in the zona glomerulosa of the adrenal glands (Holland et al. 1995). Aldosterone stimulates reabsorption of Na<sup>+</sup> and secretion of potassium by principal cells in the collecting duct. In turn, retained Na<sup>+</sup> is responsible for increased extracellular fluid volume that increases BP. Secretion of aldosterone is stimulated by high plasma potassium concentration and adrenocorticotrophic hormone (ACTH), and inhibited by atrial natriuretic peptide (ANP) (Vinson et al. 1991; Himathongkam et al. 1975; Chartier and Schiffrin 1987). Aldosterone-dependent Na<sup>+</sup> reabsorption is due to the upregulation of epithelial Na<sup>+</sup> channel- $\alpha$  (alfa) (ENaC $\alpha$  (alfa)) subunit gene expression and increased apical density of ENaC channels due to serum- and glucocorticoid-induced kinase-1 (Sgk1)-induced disinhibition of Nedd4-2-triggered internalization and degradation of ENaC (Debonneville et al. 2001). Aldosterone downregulates the expression of histone H3 methyltransferase Dot1a and the DNA-binding protein Af9 complexed with chromatin within the ENaC $\alpha$  (alfa) 5'-flanking region (Zhang et al. 2007). In addition, aldosterone-induced Sgk1 phosphorylates Ser435 of Af9, causing disruption of the protein-protein interactions of Dot1a and Af9. This results in hypomethylation of histone H3 Lys79 and release of transcriptional repression of the *ENaCab* gene. Important role of aldosterone in childhood hypertension is underscored by the ability of mineralocorticoid receptor antagonists not only to effectively reduce elevated BP due to hyperaldosteronism (e.g., adrenal hyperplasia), but to

**Table 2** Effect of genetic inactivation of the renin-angiotensin-aldosterone system genes in mice on the renal and blood pressure phenotype

Gene	Function of gene	Renal phenotype	Blood pressure	References
<i>AGT</i>	Renin substrate	Vascular thickening Interstitial fibrosis Delayed glomerular maturation Hypoplastic papilla Hydronephrosis Reduced ability to concentrate urine	Very low	Hirsch et al. (2006), Iwai and Inagami (1992), Jung et al. (1993), Nagata et al. (1996), Tanimoto et al. (1994)
<i>Renin</i>	Enzyme that generates ANG I from AGT	Arterial wall thickening Interstitial fibrosis Glomerulosclerosis Hypoplastic papilla Hydronephrosis	Very low	Song et al. (2016), Takahashi et al. (2005)
<i>ACE</i>	Enzyme that generates ANG II from ANG I	Arterial wall thickening Hypoplastic papilla and medulla Hydronephrosis Reduced ability to concentrate urine	Very low	Kakuchi et al. (1995)
<i>AT<sub>1A/B</sub></i>	Ang II receptor	Decreased kidney weight Delayed glomerular maturation Arterial wall thickening Interstitial fibrosis Tubular atrophy Hypoplastic papilla and medulla Hydronephrosis Reduced ability to concentrate urine	Very low	Longo et al. (2005), Lopez et al. (2001), Tsuchida et al. (1998)
<i>AT<sub>1A</sub></i>	Ang II receptor	Normal or mild papillary hypoplasia	Moderately low	Huh et al. (2008)
<i>AT<sub>1B</sub></i>	Ang II receptor	Normal	Normal	Knowles et al. (2001), Chen et al. (1997)
<i>AT<sub>2</sub></i>	Ang II receptor	Duplicated ureters Hydronephrosis	High	Holland et al. (1995), Niimura et al. (1995), Hein et al. (1995), Oshima et al. (2001)
<i>PRR</i>	Renin/prorenin receptor	Decreased ureteric bud branching and nephron number, renal hypoplasia	Unknown	Zhong et al. (2004), Zhou et al. (2004)

offer survival benefits in heart failure and augment potential for renal protection in proteinuric chronic kidney disease.

## Glucocorticoids

Glucocorticoids are vital for normal development and control of hemodynamic homeostasis. Cortisol or dexamethasone infusion increases BP in the

fetal sheep (Tangalakis et al. 1992; Fletcher et al. 2002). Dexamethasone increases BP in wild type serum and glucocorticoid inducible kinase (Sgk) *Sgk1*<sup>+/+</sup> mice but not in *Sgk1*<sup>-/-</sup> mice (Boini et al. 2008), indicating that hypertensinogenic effects of glucocorticoids on BP are mediated, at least in part, via Sgk1. A higher ratio of cortisol to cortisone in venous cord blood is associated with higher systolic blood pressure later in life in humans (Huh et al. 2008), suggesting that

increased fetal glucocorticoid exposure may account for higher systolic BP in childhood. However, no differences in BP and cardiovascular function are detected at school age in children treated as neonates with glucocorticoids for chronic lung disease (de Vries et al. 2008). It is possible that the functional consequences of glucocorticoid therapy during neonatal life may manifest only later in life. Deleterious effects of elevated endogenous glucocorticoids on childhood BP are apparent, for example, in Cushing's disease or glucocorticoid-remediable aldosteronism.

### Kallikrein-Kinin System

The kallikrein-kinin system (KKS) is another group of proteins that plays an important role in the regulation of blood pressure. Kinins, including bradykinin (BK), are formed from kininogen by the kininogenase tissue kallikrein (Pesquero and Bader 1998) (Fig. 3). Bradykinin is degraded by ACE-kininase II, the enzyme that also converts Ang I to Ang II (Erdös and Oshima 1974). Kinins act by binding to B1 ( $B_1R$ ) and B2 ( $B_2R$ ) receptors. The  $B_1R$  is activated by Des-Arg<sup>9</sup>-BK produced from BK by kininase I and mediates tissue injury and inflammation (Marceau et al. 1998). The renal and cardiovascular effects of BK are mediated predominantly by the  $B_2R$ . Kininogen is expressed in the ureteric bud and stromal interstitial cells of the E15 metanephros in the rat (El-Dahr et al. 1993). Following completion of nephrogenesis, kininogen is localized in the collecting duct. The main kininogenase, true tissue kallikrein, is encoded by the *KLK1* gene (Clements 1994). Transcription of the *KLK1* gene is regulated by salt and protein intake, insulin, and mineralocorticoids. Expression of the renal *KLK1* gene is suppressed in chronic phase of renovascular hypertension (El-Dahr et al. 1993).

In the developing rat kidney, kallikrein mRNA and immunoreactivity are present in the connecting tubule (El-Dahr et al. 1998). In the mature kidney, tissue kallikrein mRNA is expressed in the distal tubule and glomeruli (Xiong et al. 1989). Thus, BK can be generated intraluminally from kininogen

present in the collecting duct or in the interstitium. BK generated intraluminally causes natriuresis, whereas interstitial BK may regulate medullary blood flow (Siragy 1993). The proximity of the distal tubule to the afferent arteriole may allow kallikrein or BK to diffuse from the distal tubular cells and act in a paracrine manner on the preglomerular microvessels (Beierwaltes et al. 1985). The human  $B_1R$  and  $B_2R$  genes are located on chromosome 14 and demonstrate 36% genomic sequence homology (McEachern et al. 1991). Both  $B_1R$  and  $B_2R$  are members of the seven transmembrane GPCR family. During metanephrogenesis, the  $B_2R$  is expressed in on both luminal and basolateral aspects of collecting ducts suggesting that activation of  $B_2R$  is important for renal tubular growth and acquisition of function (El-Dahr et al. 1997). The expression of  $B_1R$  is inducible rather than constitutive. In contrast to  $B_2R$ ,  $B_1R$  is not expressed in significant levels in normal tissues (Marceau et al. 1998). Although BK does not appear to be a primary mediator of the maturational rise in RBF in the rat, its vasodilatory effects in the developing kidney are tonically antagonized by Ang II AT<sub>1</sub>R (El-Dahr et al. 1995). Stimulation of the  $B_2R$  during adult life stimulates production of nitric oxide and prostaglandins resulting in vasodilation and natriuresis (Siragy 1993). The importance of the KKS in the regulation of BP is underscored by the finding of elevated BP in mice that lack the  $B_2R$  (Beierwaltes et al. 1985). Moreover,  $B_2R$ -null mice are prone to early onset of salt-sensitive hypertension (Cervenka et al. 1999). Interestingly,  $B_1R$  receptor blockade in  $B_2R$ -null mice produces a significant hypertensive response (Duka et al. 2003), indicating that both receptors participate in the development of hypertension. In keeping with this hypothesis, single-nucleotide polymorphisms in the promoters of both  $B_1R$  and  $B_2R$  genes have been reported to be associated with hypertension in African-Americans, demonstrating that the two receptors play a role in BP homeostasis in humans (Cui et al. 2005). The direct potential role of the KKS in childhood hypertension is further highlighted by studies showing that endogenous bradykinin contributes to the beneficial effects of ACE inhibition on BP in humans (Gainer et al. 1998).



## Arginine Vasopressin

Arginine vasopressin (AVP), also known as anti-diuretic hormone (ADH), is synthesized in the hypothalamus and released in response to increased plasma osmolality, decreased arterial pressure, and reductions in circulating blood volume. Three subtypes of vasopressin receptors,  $V_1R$ ,  $V_2R$ , and  $V_3R$ , mediate vasoconstriction, water reabsorption, and central nervous system effects, respectively. In addition, stimulation of the  $V_2R$  induces endothelial NOS expression and promotes NO production in the renal medulla which attenuates the  $V_1R$ -mediated vasoconstrictor effects (Szentivanyi et al. 2000). In adult species, AVP supports arterial BP when both the sympathetic system and the RAAS are impaired by sympathetic blockade (Peters et al. 1990). Treatment with a  $V_1R$  antagonist has no effect on arterial BP in fetal sheep (Ervin et al. 1992; Tomita et al. 1985). In contrast, antagonism of the  $V_1R$  during hypotensive hemorrhage impairs the ability of the fetus to maintain BP (Kelly et al. 1983). Thus, endogenous AVP has little impact on basal hemodynamic homeostasis of the fetus, but plays an important role in vasopressor response to acute stress such as hemorrhage.

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## Endothelium-Derived Vasoactive Factors

### Nitric Oxide

Hypertension is associated with abnormal endothelial function in the peripheral, coronary, and renal vasculature. Nitric oxide (NO) is an important mediator of endothelium-dependent vasodilation. NO enhances arterial compliance, reduces peripheral vascular resistance, and inhibits proliferation of vascular smooth muscle cells (Cowley et al. 2003). The major source of NO production in the rat kidney is the renal medulla, where NO regulates medullary blood flow, natriuresis, and diuresis (Goldblatt et al. 1934; Jin et al. 2004). NO promotes pressure natriuresis via cGMP (Taddei et al. 1996a). The effects of Ang II or AVP on medullary blood flow are buffered by

the increased production of NO (Goldblatt et al. 1934), indicating that endogenous NO tonically counteracts the effects of vasoconstrictors within the renal medullary circulation. Interestingly, endothelial dysfunction is not only a consequence of hypertension, but may predispose to the development of hypertension. In this regard, impaired endothelium-dependent vasodilation has been observed in normotensive children of patients with essential hypertension as compared with those without a family history of hypertension (Taddei et al. 1996b), demonstrating that an impairment in NO production precedes the onset of essential hypertension. Acute antagonism of NO generation leads to an increase in BP and decreases RBF in the fetal sheep (Yu et al. 2002). In fetal rat kidneys, endothelial NO synthase (eNOS) immunoreactivity is first detected in the endothelial cells of the intrarenal capillaries on E14 (Han et al. 2005). These findings suggest that eNOS may play a role in regulating renal hemodynamics during fetal life. Moreover, eNOS-knockout mice exhibit abnormal aortic valves, congenital atrial, and ventricular septal defects, indicating that eNOS-derived NO plays an important role in the development of the circulatory system (Teichert et al. 2008). The effect of intrarenal infusion of the NO antagonist L-NAME on decreases in RBF and GFR is more pronounced in the newborn than in the adult kidney (Solhaug et al. 1996). These effects of NO may act to oppose high RAAS activity present in the developing kidney. Similar to NO, hydrogen sulfide ( $H_2S$ ) is a gasotransmitter that has been recently revealed as playing a role in cardiovascular physiology.  $H_2S$ -knockout mice develop age-dependent hypertension, whereas administration of  $H_2S$  donors attenuates the hypertensive response via decreased renin production in a rat two-kidney one-clip renovascular hypertension model (Yang et al. 2008; Lu et al. 2010).

### Asymmetrical Dimethylarginine

Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of eNOS (Kielstein and Zoccali 2005). Infusion of ADMA increases BP

and renal vascular resistance, and decreases renal plasma flow during adulthood (Kielstein et al. 2004). ADMA levels in fetal umbilical venous plasma are higher than in maternal plasma (Maeda et al. 2003). However, low resistance to umbilical blood flow is maintained despite substantially higher fetal ADMA levels, which, by implication, has led to speculation that NO must be a key modulator of fetal vascular tone. Hypertensive children had higher plasma ADMA levels as compared with normotensives children in one study (Goonasekara et al. 2000). In contrast, plasma ADMA levels did not differ between normotensive and hypertensive young adults (Päivä et al. 2008). Moreover, plasma ADMA correlates negatively with vascular resistance (Päivä et al. 2008), suggesting that in a physiological setting ADMA levels in people with elevated vascular tone may decrease to compensate for inappropriately high resistance.

## Endothelin

Endothelins (ETs) are vasoconstrictor peptides produced by endothelial cells (Yanagisawa et al. 1988; Lüscher et al. 1992). Three ETs have been described – endothelin-1 (ET-1), -2 (ET-2), and -3 (ET-3). The hemodynamic effects of ET-1 are mediated by ET<sub>A</sub> and ET<sub>B</sub> GPCRs. In the kidney, ET-1 mRNA is expressed in the glomeruli and medullary collecting ducts (Kohan 1999; Ujiie et al. 1992). ET receptors are located in podocytes, glomeruli, afferent, and efferent arterioles, and in the proximal tubule, medullary thick ascending limb, and collecting duct (Yamamoto et al. 2002). Activation of the ET<sub>B</sub> receptor results in natriuresis and vasodilation via release of NO and PGE<sub>2</sub>, whereas the ET<sub>A</sub> receptor mediates renal vasoconstriction (Hirata et al. 1993). In the fetal lamb, ET<sub>A</sub> and ET<sub>B</sub> receptors expressed on vascular smooth muscle cells mediate vasoconstriction, whereas ET<sub>B</sub> receptors located on endothelial cells mediate vasodilation (Arai et al. 1990; Wong et al. 1995). In the renal circulation of fetal sheep, ET-1, acting via the ET<sub>B</sub> receptor, results in vasodilation (Fujimori et al. 2005). However, ET<sub>A</sub> receptor-mediated vasoconstriction also contributes

to the regulation of the fetal renal vascular tone (Fineman et al. 1994). The critical role for the renal ET-1 and ET<sub>A</sub>/ET<sub>B</sub> receptors in the regulation of systemic BP is demonstrated by the finding of increased BP in mice with collecting duct-specific knockout of either ET-1 or both ET<sub>A</sub> and ET<sub>B</sub> receptors (Ahn et al. 2004; Ge et al. 2008). Moreover, BP in these knockouts increases further with high salt intake, indicating that combined ET<sub>A</sub>/ET<sub>B</sub> receptor deficiency leads to salt-sensitive hypertension.

## Natriuretic Peptides

Natriuretic peptides include atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), urodilatin, and dendroaspis-type natriuretic peptide (DNP) (Sudoh et al. 1990; Schweitz et al. 1992; Hirsch et al. 2006; de Bold et al. 1981). Natriuretic peptides act through binding to three guanylyl cyclase-linked receptors: NPR-A, NPR-B, and NPR-C (Levin et al. 1998). In the adult heart, ANP and BNP are stored in atrial and ventricular myocytes, respectively, released in response to atrial stretch, increased BP, atrial tachycardia, or increased osmolality (Levin et al. 1998; Brenner and Stein 1989), and are rapidly degraded in the lung and kidney by neutral endopeptidase (Roques et al. 1993). ANP and BNP decrease the secretion of renin and aldosterone, and antagonize the effects of Ang II on vascular tone and renal tubular reabsorption to cause natriuresis, diuresis, and a decrease in BP and intravascular fluid volume (Hunt et al. 1996). ANP and BNP peptide levels are higher in fetal than adult ventricles, suggesting that the relative contribution of ventricular ANP is greater during embryonic as compared to adult life (Zeller et al. 1987; Wei et al. 1987; Hersey et al. 1987). ANP and BNP mRNA is expressed on E8 in the mouse and increases during gestation, suggesting that both ANP and BNP play a role in the formation of the developing heart. Circulating ANP levels are higher in fetal as compared to adult rat or sheep (Wei et al. 1987; Cheung 1995). Infusion of ANP into the circulation of the lamb fetus decreases BP

and causes diuresis (Cheung et al. 1987). ANP secretion during postnatal development is stimulated in response to similar physiological stimuli as in the adult animal and can be induced by Ang II infusion, volume loading, hypoxia, or increase in osmolality (Cheung et al. 1987; Rosenfeld et al. 1992). Plasma levels of ANP are higher in preterm as compared with term infants (Bierd et al. 1990). In full-term infants, circulating ANP levels increase during the first week of life and decrease thereafter (Weil et al. 1986). Thus, the initial postnatal increase in ANP may mediate diuresis during the transition to extrauterine life. Subsequent decrease in plasma ANP may serve to conserve sodium, which is required for rapid growth. Although BP remains normal in BNP-null mice (Tamura et al. 2000), ANP-null mice develop hypertension later in life (John et al. 1995). Mice lacking NPR-A receptor exhibit cardiac hypertrophy and have elevated BP, indicating that the ANP and BNP play an important role in the regulation of myocyte growth and BP homeostasis during development (John et al. 1995; Knowles et al. 2001).

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### Vasoactive Factors and Developmental Programming of Hypertension

An inverse relation between birth weight or maternal undernutrition and adult BP led to the concept of developmental programming of hypertension (Barker and Bagby 2005). The tissue-specific brain RAAS was upregulated in the fetus of dams fed a low protein (LP) diet, and hypertensive adult offspring of LP-fed dams have evidence of an increased pressor response to Ang II (Pladys et al. 2004; Edwards et al. 1999). This and other studies suggest that inappropriate activation of the RAAS may link exposures in fetal life to childhood and adult hypertension. Interestingly, LP maternal diet has been reported to result in a decreased methylation of the promoter region of the *AT<sub>1B</sub>R* in offspring in the rat (Bogdarina et al. 2007). It is conceivable that epigenetic modifications of *AT<sub>1B</sub>R* gene may be one mechanism by which changes in the RAAS lead to developmental programming of hypertension. LP diet or

caloric restriction during gestation has been associated with a decrease in the renal kallikrein activity, blunted vasorelaxation to NO donor infusion, an increase in vascular superoxide anion concentration, and a decrease in superoxide dismutase activity in the offspring (Yosypiv et al. 1997; Brawley et al. 2003; Franco et al. 2002). In addition, heterozygous eNOS offspring of *eNOS*-null mothers exhibit impaired endothelium-dependent vasodilation as compared to heterozygous offspring of *eNOS*<sup>+/+</sup> mothers (Longo et al. 2005). These observations indicate that impairment in endothelium-dependent vascular function is associated with developmentally programmed hypertension and that maternal *eNOS* genotype modulates the offspring's predisposition to hypertension. Further studies are needed to establish the mechanisms by which alterations in antenatal environment impacts vasoactive factor systems and their interplay to program hypertension during postnatal life.

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### Urotensin II

Human urotensin-II (U-II) is an 11-amino acid cyclic peptide cleaved from a larger prepro-U-II precursor peptide of about 130 amino acids (Coulouarn et al. 1998). The U-II receptor is a seven-transmembrane, G protein-coupled receptor encoded on chromosome 17q25.3 in humans (Ames et al. 1999). Ligand binding of the receptor results in G protein-mediated activation of PKC, calmodulin, and phospholipase C. There is also evidence that links the MAP kinases ERK1/2, the Rho kinase pathway, and peroxisome proliferator-activated receptor  $\alpha$  in the intracellular signaling cascade after the U-II receptor is activated. Human prepro-U-II mRNA is expressed in the brain, spinal cord, kidney, spleen, small intestine, thymus, prostate, pituitary, and adrenal gland (Coulouarn et al. 1998). U-II is the most potent mammalian vasoconstrictor identified to date and is tenfold more potent than endothelin-I in the isolated rat thoracic aorta. (Ames et al. 1999). It circulates in the plasma of healthy individuals, and acts as a circulating vasoactive hormone and as a locally acting paracrine or autocrine factor in

cardiovascular regulation (Affolter and Webb 2001; Totsune et al. 2001).

The kidney is a major site of U-II production and urinary concentrations of U-II in humans are approximately three orders of magnitude higher than plasma concentrations (Matsushita et al. 2001). In the kidney, U-II is present in the smooth muscle cells and endothelium of arteries, proximal convoluted tubules, and particularly the distal tubules and collecting ducts (Shenouda et al. 2002). Changes in the concentration of U-II in the plasma and urine have been found in a number of diseases. Plasma U-II is elevated in hypertensive adult patients compared to normotensive controls and correlates with the severity of hypertension (Cheung et al. 2004; Zhu et al. 2015), suggesting that U-II may have a role in hypertension in humans. Higher urinary U-II levels have been reported in adult patients with essential hypertension, glomerular disease, and renal tubular disorders, but not in normotensive patients with glomerular disease (Matsushita et al. 2001). Plasma immunoreactive U-II levels are increased in children with congenital heart disease (CHD) and concentrations increase further after cardiopulmonary bypass (CPB) (Simpson et al. 2006). Thus, U-II may be an important mediator in the cardiovascular dysfunction that affects children with CHD early after CPB. Animal studies demonstrated that enhanced tonic UT-II activation may contribute to renal dysfunction in prehypertensive spontaneously hypertensive rats (SHR) (Forty and Ashton 2013).

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## Renalase

Renalase, an amine oxidase expressed in the kidney, heart, liver, and brain metabolizes catecholamines. Anesthetized BP and heart rate are reported as higher in renalase-null as compared to wild-type littermates (Barker and Bagby 2005). Available data suggest that renalase deficiency is associated with increased sympathetic tone and resistant hypertension (Wu et al. 2011). Further, recombinant renalase has potent antihypertensive properties;

given those properties it may have potential as an antihypertensive medication, though studies remain to be carried out (Desir 2012).

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## Summary

Various vasoactive substances regulate cardiovascular homeostasis during development, and new ones are still being discovered. Many cardiovascular factors exert pleiotropic actions both systemically and within diverse organ systems. Continuous discovery of new vasoactive substances and more complete knowledge of their role during development improve our understanding of the developmental origin of hypertension and cardiovascular disease and help to minimize their impact on the nation's health. Further work is needed to more precisely define the role of emerging cardiovascular regulatory factors and their growing relevance to a number of conditions in animal models of human disease and in human diseases including hypertension.

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## Cross-References

- ▶ [Endothelial Dysfunction and Vascular Remodeling in Hypertension](#)
- ▶ [Ions and Fluid Dynamics in Hypertension](#)
- ▶ [Neurohumoral and Autonomic Regulation of Blood Pressure](#)
- ▶ [Perinatal Programming of Arterial Pressure](#)

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Albert P. Rocchini

## Abstract

The regulation of the heart and the vasculature are linked by two fundamental principles – that the metabolic state of each organ or tissue is dependent on the relationship between metabolism and blood flow and that each organ or tissue has the ability to control its own blood flow according to local metabolic and functional needs. On a whole-body level, these principles are mediated through blood pressure homeostasis (a closed negative feedback loop that regulates mean arterial pressure around a set reference level). Mean systemic arterial pressure is defined as the product of the sum of all regional blood flows (cardiac output) and the parallel sum of all regional vascular resistances (total systemic vascular resistance). The current chapter discusses the main factors that regulate both cardiac output and systemic vascular resistance and how they relate to the potential pathogenesis of systemic hypertension.

## Keywords

Blood pressure homeostasis • Afterload • Contractility • Preload

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## Introduction

Understanding normal cardiovascular physiology is critical in order to adequately understand both the pathophysiology of systemic hypertension and the management of the pediatric patient with hypertension. The current chapter will discuss the main factors that regulate both cardiac output and systemic vascular resistance. (For additional physiology concerning BP, see Part I, “Regulation of Blood Pressure and Pathophysiologic Mechanisms of Hypertension”, ► Chaps. 1, “Neurohumoral and Autonomic Regulation of Blood Pressure,” ► 2, “Vasoactive Factors and Blood

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Pressure in Children,” and ► 4, “Ions and Fluid Dynamics in Hypertension.”)

The regulation of the heart and the vasculature is connected by two fundamental principles – first, that the metabolic state of each tissue/organ is dependent on the relation between metabolism and blood flow and, second, that each tissue and organ has the ability to regulate its own blood flow according to local metabolic and functional needs.

The primary role of the cardiovascular system is to deliver sufficient oxygen to meet the metabolic needs of the body’s tissues. Oxygen delivery is proportional to tissue blood flow, and there are three basic equations that determine tissue blood flow. The first is based on Ohm’s law for fluids (Hall 2012) – blood flow through any tissue is equal to the pressure gradient across the tissue divided by the vascular resistance of the tissue/organ. For the cardiovascular system on a macro-level, Ohm’s law for fluids would be that whole-body flow (cardiac output (CO)) is equal to driving pressure (mean arterial blood pressure (MAP)) minus venous pressure, but since venous pressure is relatively small, it is usually omitted. Thus,

**Equation I : Ohm’s Law for Cardiovascular System**

$$: CO = \frac{MAP}{SVR}$$

The second equation states that cardiac output is equal to the product of heart rate (HR) and stroke volume (SV).

**Equation II : CO = HR × SV**

Third, stroke volume is the difference between end-diastolic volume (EDV) and end-systolic volume (ESV).

**Equation III : SV = EDV – ESV**

The local control of tissue/organ flow (autoregulation) involves both short-term and long-term mechanisms. The short-term mechanisms can be activated within seconds to cause

vasoconstriction or dilation of the local vasculature and are usually mediated either by metabolic waste products, endothelial mechanisms, or myogenic responses. Long-term blood flow regulation takes place over days to weeks and involves structural changes in the blood vessels such as increasing or decreasing the width of vessel walls and/or increasing or decreasing number of capillaries. Since regional blood flows are difficult to clinically measure, differ widely, and in some cases are highly variable, most clinicians tend to concentrate more on whole-body measures of flow, pressure, and resistance. On a macro level, whole-body autoregulation can be viewed as a major determinant of systemic blood pressure homeostasis (Coleman et al. 1971).

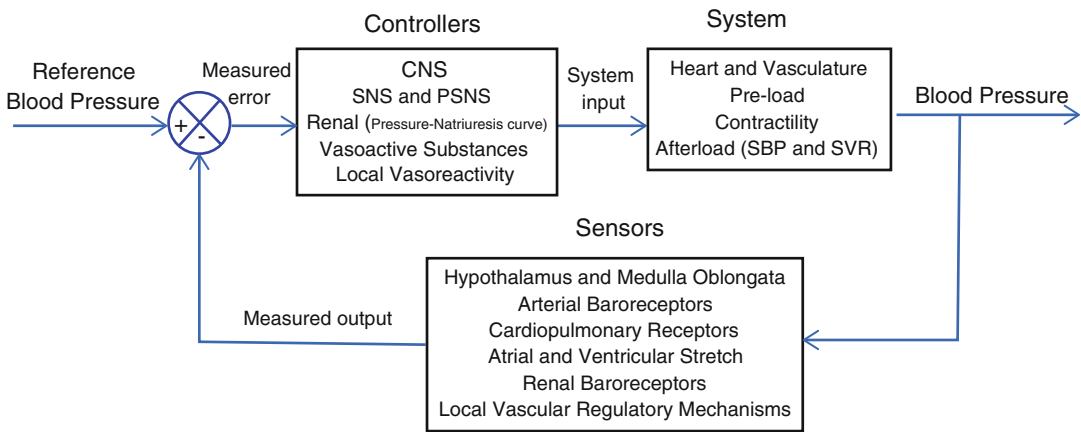
Blood pressure homeostasis is accomplished through a closed negative feedback loop. Figure 1 schematically depicts the concept of a closed negative feedback loop. The loop is negative, since the sensed value is subtracted from the desired value (reference value) to create the error signal, which is then applied to get the system back to its reference level. For blood pressure homeostasis, the controllers are the determinants of mean arterial pressure, while the system is the heart and vasculature, and the sensors are the physiologic monitors of the system output (mean arterial pressure) that send data back to the controllers to adjust the determinants of mean arterial pressure.

Systemic mean arterial pressure is defined as the product of the sum of all regional blood flows (cardiac output) and the parallel sum of all regional vascular resistances (total systemic vascular resistance). Therefore, in order to understand how systemic mean blood pressure is modulated, it is necessary to understand what regulates both cardiac output and systemic vascular resistance.

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## Cardiac Output

Regardless of age, the major determinants of cardiac output are preload, afterload, contractility, and heart rate (Anderson et al. 1982; Thornburg and Morton 1986). At all ages, increasing the inotropic state of the heart has a positive effect



**Fig. 1** A schematic illustration of a closed feedback loop to control mean arterial pressure (MAP) around a reference level (set point). The reference (basal MAP) is defined as the external input of the system. The controllers (physiologic determinants of MAP) manipulate the inputs to the system (heart and vasculature) to obtain the desired effect on the system output (MAP). The sensors (physiologic

monitors of MAP) subtract the system output from the desired reference value and either amplify or suppress the controllers to maintain the system output (MAP) to reference levels. (Abbreviations: *CNS* central nervous system, *SNS* sympathetic nervous system, *PSNS* parasympathetic nervous system, *SVR* systemic vascular resistance, and *SBP* systolic blood pressure)

on cardiac function, whereas increasing afterload has a negative effect. However, when dealing with the response of the whole body, it is almost impossible to only change one of these variables without also affecting another variable in kind. Thus the net physiological response is the combined effect of the intervention on *several* variables. For example, in the isolated papillary muscle, an increasing rate of muscle stimulation (i.e., increasing the “heart rate” variable) *always* results in an increase in the force of contraction (Anderson et al. 1982). However, in children, pacing the heart at incrementally faster rates causes a decrease in stroke volume and no change or even a slight decrease in cardiac output. The opposite effects seen *in vivo* are the result of a complex interaction of venous return, ventricular end diastolic volume, inotropic state, heart rate, and afterload.

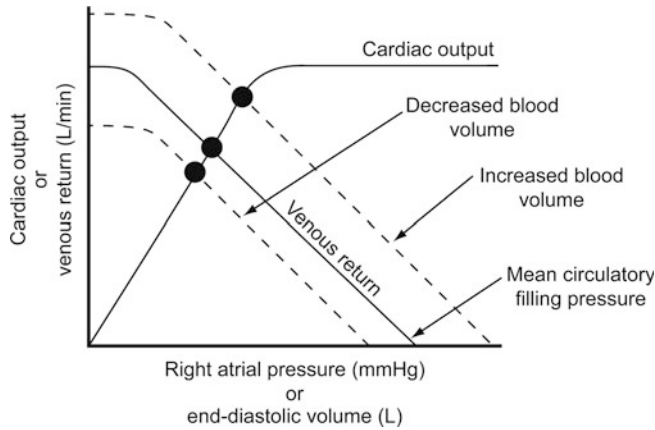
## Preload

From a clinical standpoint, preload is defined as ventricular end-diastolic volume/pressure or atrial filling pressure. The Frank-Starling mechanism (Starling 1915) describes the ability of the heart to increase its cardiac output as end-diastolic

volume increases (Fig. 2). The physiological basis of the Frank-Starling mechanism is that as end-diastolic volume increases, myocyte sarcomere length is increased, causing an increase in contractile forces and a resultant increase in cardiac output. Two of the major determinants of preload are circulating blood volume and venous tone.

## Venous Tone

Short-term changes in preload can be mediated through changes in venous tone (venous compliance). Venous compliance can be acutely affected by sympathetic mediated vasoconstriction, angiotensin II, respiratory activity, hydrostatic forces, and contraction of skeletal muscles. Clinically, venodilator drugs (such as nitroglycerin, angiotensin-converting enzyme inhibitors,  $\alpha$ -receptor blockers, etc.) increase venous compliance and therefore are used to treat acute heart failure, pulmonary edema, and angina by acutely reducing preload. With exercise, venous compliance acutely decreases in an attempt to increase venous return to the heart (preload) and thereby increase cardiac output. The exercise-induced decrease in venous compliance occurs since the veins in the limbs and abdomen are situated between skeletal



**Fig. 2** Graphical analysis of Guyton's classic cardiac function curve and the venous return curve. The graph consists of simultaneous plots of cardiac output and venous return as a function of left ventricular end-diastolic volume or right atrial pressure. The solid dot represents the steady state where the two curves intersect (i.e., the point where cardiac output is equal to venous return). MCFP (mean circulatory filling pressure) represents the degree of filling of the whole circulation (the theoretical atrial pressure when cardiac output is zero) and relates blood volume to vascular capacity. The three curves represent the effect of

blood volume on cardiac output. The center venous return curve represents the relationship at normal blood volume. With an increased blood volume and/or a decrease in venous compliance, the venous return curves shifts in a parallel manner to the right resulting in both an increase in cardiac output and right atrial pressures. Similarly with decrease in blood volume and/or an increase in venous compliance, the venous return curve shifts to the left resulting in both a decrease in cardiac output and right atrial pressure (Adapted from Montani and Van Vliet) (Montani and van Vliet 2009).

muscles. When the skeletal muscles contract and relax, they compress the veins thereby decreasing venous compliance. It is also known that the duration of venoconstriction after exercise relates to the length of exercise and appears to be independent of sympathetic activity (Sharpey-Schafer 1963).

### Circulating Blood Volume

Long-term changes in preload are caused by changes in circulating blood volume. From the heart's standpoint, acute changes in preload (i.e., right and left ventricular volume/filling pressure) result in both changes in activation of the cardiopulmonary baroreceptors, which in turn change both sympathetic and parasympathetic tone, and changes in the release and production of natriuretic peptide, which is stimulated by distention of the atria and ventricles.

### Cardiopulmonary Baroreceptors

The cardiopulmonary baroreceptors consist of a set of sensory afferent fibers that respond to changes in central volume. The afferent fibers

arise from the left ventricle, left atrium, and pulmonary veins and travel via the vagus nerve to afferent cell bodies in the nodose ganglia. The afferent cell bodies in the nodose ganglia send projections to the nucleus tractus solitarius in the medulla that modulates the sympathetic nerve traffic from the brain. The cardiopulmonary baroreceptors exert minimal effects on the parasympathetic nervous system.

### Natriuretic Peptides

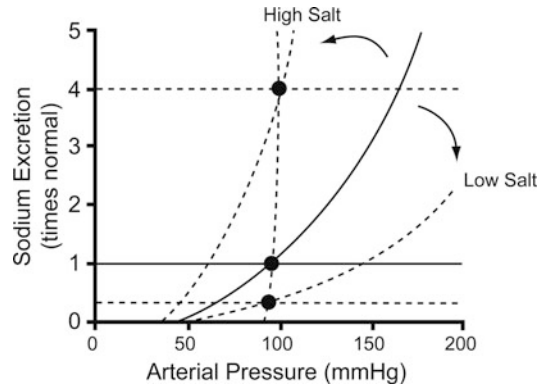
The natriuretic peptides are a family of peptide hormones that are synthesized and secreted by the heart, brain, and other organs. The stimulus for release of these hormones by the heart is atrial or ventricular distention and/or neurohumoral stimuli. Atrial natriuretic peptide, the first of this peptide family to be identified, is a 28 amino acid peptide that is synthesized, stored, and released by atrial myocytes (de Bold 1985). Brain natriuretic peptide is a 32 amino acid peptide that was originally identified in the brain but is predominantly located within the cardiac ventricles. The stimuli for

release of both peptides are atrial or ventricular distention and stretch, sympathetic stimulation of  $\beta$ -adrenoceptors, angiotensin II, and endothelin (Widmaier 2008). There are three types of natriuretic peptide receptors, NPR-A, NPR-B, and NPR-C. Binding of the natriuretic peptide to its receptor (either NPR-A or NPR-B) causes the conversion of GTP (guanosine triphosphate) to cGMP (cyclic guanosine monophosphate). cGMP activates a cGMP-dependent kinase that phosphorylates proteins that produce the following physiological responses – in the kidney, dilation of afferent glomerular arterioles resulting in increased glomerular filtration rate and decreased sodium reabsorption in the distal convoluted tubule and cortical collecting ducts, which results in a greater excretion of sodium and water and a decrease in renin release; in the adrenal gland, reduction in aldosterone secretion; in the vascular system, relaxation of vascular smooth muscle in arterioles and venules; and in adipose tissue, an increase in the release of free fatty acids.

Natriuretic peptide receptor-C (NPR-C) functions mainly as a clearance receptor by binding and sequestering atrial and brain natriuretic peptide from the circulation. The chronic increase in circulating blood volume observed in obesity is, in part, associated with an increase in NPR-C in adipose tissue, leading to enhanced adipose-mediated clearance of natriuretic peptides and a concomitant reduction in circulating natriuretic peptide levels (Sarzani et al. 1995). Brain natriuretic peptide (BNP) is useful from both a diagnostic and therapeutic standpoint. For example, diagnostically, in patients with congestive heart failure, BNP levels are usually greater than 100 pg/ml (Atisha et al. 2004). Therapeutically, a recombinant form of BNP (nesiritide) has been used to treat refractory congestive heart failure (Colucci et al. 2000).

### The Kidney and Blood Volume

Both changes in autonomic tone and natriuretic peptide levels affect the control of salt and water excretion by the kidney. In most clinical situations, both short-term and long-term changes in preload are regulated, based on the relationship



**Fig. 3** Graphical representation of the concept of renal pressure-natriuresis and how adjustments of this relationship are affected by changes in salt intake. The *solid dots* represent the equilibrium point between mean arterial pressure and salt excretion. The *solid middle curve* represents the pressure-natriuresis relations for normal sodium intake. The pressure-natriuresis curve adjusts with varying salt intakes (left shift with steepening at high-salt intake, right shift with flattening at low-salt intake). If you were to join all of the *solid dots*, an almost vertical chronic pressure-natriuresis relationship would be depicted. Therefore, modulation of the pressure-natriuresis curves during alternations in salt intakes allows the body to achieve sodium balance with minimal changes in arterial pressure (Adapted from Montani and Van Vliet) (Montani and van Vliet 2009).

of urinary sodium excretion as a function of arterial pressure (pressure-natriuresis relationship) (Guyton et al. 1972a, b). Figure 3 depicts the relation between arterial pressure and sodium excretion under conditions of normal, high, and low sodium intake. As can be seen in the figure, with changing salt intake, adjustments in the pressure-natriuresis curve occur (a left shift with a high-salt intake and a right shift with a low-salt intake), allowing the body to achieve sodium balance with minimal changes in arterial pressure. A number of neurohormonal mechanisms (renal sympathetic nerve activity, natriuretic and antinatriuretic hormones, and the renin-angiotensin-aldosterone system) help to adjust the pressure-natriuresis curve to varying salt intakes. Importantly, the changes in the pressure-natriuresis curve induced by salt in the diet occur in the setting of autoregulation of both renal blood flow and glomerular filtration rate. Therefore, it is the pressure-natriuresis relationship that links mean arterial pressure to sodium balance.

### Chronic Changes in Preload and Hypertension

A chronic increase in cardiac preload, which occurs as a consequence of a chronic increase in circulating blood volume, leads to systemic hypertension. For example, obesity-associated hypertension is in large part believed to be related to a chronic change in the renal function relationship that leads to a chronic increase in circulating blood volume, cardiac preload, and cardiac output (Rocchini et al. 1989). Similarly, end-stage renal disease also is associated with chronic volume expansion and hypertension.

### Cardiac Contractility

The second determinant of cardiac output is cardiac contractility, the intrinsic ability of the heart to contract independent of the influences of either preload or afterload. The ability to produce force during contraction depends on the incremental degrees of binding between myosin and actin filaments (Hall 2012). The degree of binding that occurs is directly related to the intracellular concentration of calcium. The normal way that the heart changes its contractile state is through modulation of the sympathetic nervous system. Increased sympathetic tone results in catecholamines (norepinephrine and epinephrine) released from sympathetic nerve terminal and the adrenal gland activating the beta-adrenergic receptors, which ultimately increase cytosolic calcium concentration and thereby increasing contractile force. At any given preload and afterload, an increase in contractility will cause an increase in cardiac output and a resultant increase in blood pressure. Contractility may be iatrogenically altered by the administration of inotropic agents (i.e., norepinephrine, epinephrine, dopamine, dobutamine, milrinone, etc.)

### Chronic Changes in Contractility and Hypertension

A primary increase in cardiac output may be the antecedent of essential hypertension. In 1957, Widimsky et al. (1957) reported that cardiac output was significantly increased in a group of

young patients with borderline hypertension. Others have confirmed that observation (Frohlich et al. 1970; Julius et al. 1971a, b; Messerli et al. 1981). Julius also reported that the early phase of hypertension is characterized by a hyperkinetic circulation caused by excessive sympathetic drive and a decrease in parasympathetic inhibition to the heart. Julius (Julius 1988; Julius et al. 1991a, b) demonstrated that in the later phases of hypertension, the cardiac output becomes normal but the hypertension is still neurogenic, as demonstrated by the fact that combined pharmacologic parasympathetic and beta- and alpha-adrenergic inhibition normalizes the blood pressure. Further, Stern et al. (Stern et al. 1992) showed that patients with hyperdynamic circulation also display many of the features of the insulin resistance syndrome.

### Afterload

The third determinant of cardiac output is afterload, the tension or stress developed in the wall of the ventricle. The major components of afterload are systolic aortic pressure and/or the pressure in the ventricle and the volume of the ventricle. More, precisely, afterload is related to ventricular wall stress ( $\sigma$ ) where:

$$\sigma \propto \frac{P \times r}{h}$$

( $P$  systolic ventricular pressure,  $r$  radius of the ventricle,  $h$  wall thickness).

Unless aortic stenosis is present, the pressure that the ventricle generates during ejection is aortic pressure (or systolic blood pressure). The relationship for wall stress is similar to Laplace's law, which states that the tension on the myofibrils within the ventricular wall is proportional to the pressure times the radius. Therefore, wall stress is wall tension divided by the wall thickness.

Afterload is increased when either aortic systolic pressure or systemic vascular resistance is increased. When afterload increases, there is an increase in end-systolic volume and a decrease in stroke volume and cardiac output.



The physiological basis for the increase in end-systolic volume with an increase in afterload is that an increase in afterload decreases the velocity of fiber shortening, which reduces the rate of ventricular ejection, resulting in more blood left in the ventricle at the end of systole. Therefore, although afterload per se does not alter preload, the resultant increase in end-systolic volume results in a secondary increase in preload. This interaction between preload and afterload is the basis of the treatment of heart failure with vasodilators, such as converting enzyme inhibitors or angiotensin receptor blockers. Since the vasodilators decrease arterial pressure, the ventricle can then eject blood faster, which results in an increase in cardiac output and a resultant decrease in end-systolic volume. Since less blood remains in the ventricle after systole, the ventricle will fill to a smaller end-diastolic volume (preload) than before the reduction in afterload. Long-term cardiac output remains increased because the reduction in end-diastolic volume is less than the reduction in end-systolic volume.

### **Chronic Increase in Afterload and Myocardial Hypertrophy**

Since myocyte contraction is the primary determinant of myocardial oxygen consumption, wall tension or stress and myocardial oxygen consumption are closely related (Strauer et al. 1977). Since a hypertrophied ventricle reduces wall stress and afterload, hypertrophy can be viewed as a mechanism that permits a chronically afterloaded ventricle to reduce its oxygen requirement. In patients with chronic hypertension, Laine et al. (Laine et al. 1999) demonstrated that left ventricular hypertrophy is a compensatory mechanism by the heart to normalize myocardial oxygen consumption; however, this hypertrophy occurs at the expense of a decrease in the ratio between cardiac work and oxygen consumption (efficiency). Ultimately the decrease in myocardial efficiency may predispose hypertensive patients with left ventricular hypertrophy to develop heart failure.

Hypertension is the most common risk factor and principal forerunner of heart failure (Levy et al. 1996). The majority of hypertensive patients

have heart failure with preserved ventricular function (diastolic heart failure). The compensatory left ventricular hypertrophy that accompanies hypertension adversely affects the passive portion of the left ventricular diastolic pressure-volume relationship and results in a decrease in left ventricular compliance. A normal left ventricular pressure-volume curve allows increases in left ventricular filling in the normal physiological range without clinically significant changes in left ventricular end-diastolic pressure. The decreased left ventricular compliance seen in patients with chronic hypertension causes a shift of the diastolic pressure-volume curve upward and to the left resulting in a higher left ventricular end-diastolic pressure to fill the left ventricle to the same volume as an individual with a normal left ventricular compliance. This higher left ventricular end-diastolic pressure eventually leads to pulmonary congestion, dyspnea, and other symptoms of heart failure (Kitzman et al. 1991).

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### **Determinants of Systolic, Diastolic, and Mean Blood Pressure**

The two major components of arterial pressure are mean arterial pressure and pulse pressure. Mean arterial pressure is the integrated mean of the phasic arterial waveform. It represents the steady-state component of pressure and is closely related to systemic vascular resistance. Pulse pressure depends on both left ventricular ejection and aortic impedance. In the presence of a constant cardiac output and heart rate, pulse pressure is a surrogate measurement of central aortic elastic stiffness. As central aortic stiffening increases, pulse pressure rises, systolic pressure rises, and diastolic pressure decreases. The elastic nature of the arterial wall depends on the composition and arrangement of materials that make up the media (Mceniery et al. 2005). In young persons, the thoracic aorta contains a predominance of elastin over collagen; however, as one moves more distally in the arterial tree, collagen predominates over elastin, leading to a stiffer distal vasculature. Since the arterial pulse wave travels both forward to the periphery and backward from the periphery

to the heart, the morphology of the arterial waveform results from the summation of the forward and backward waves. Variable overlap between the forward and backward waves contributes to variable augmentation of the pressure waveform. This variable pulse pressure amplification causes central aortic pulse pressure to be lower than peripheral arterial pulse pressure. This variable pulse pressure amplification explains why normal children and adolescents usually have higher leg systolic blood pressure than arm systolic blood pressure; however, it is important to remember that mean arterial pressure is the same throughout the large arteries. As we age, the aorta loses some of its elastin and becomes stiffer and more like the distal arterial tree, and this variable pulse pressure amplification disappears (Mitchell et al. 2004). Since pulse waves travel faster in stiffer arteries, pulse wave velocity is a useful clinical marker for large artery stiffness and vascular disease. In both children and adults, increased pulse wave velocity has been shown to be a predictor of cardiovascular morbidity and mortality (Franklin et al. 2005; Urbina et al. 2011; Stergiou et al. 2010; Reusz et al. 2010). In fact, because the traditional end points of stroke, myocardial infarction, and mortality used in studies in adults are unsuitable to evaluate the risk and benefits of pediatric clinical trials, pulse wave velocity has been recommended as a useful maker of predicting future cardiovascular disease in pediatric populations (Reusz et al. 2010; Urbina et al. 2009). Stiffer large arteries can also influence ventricular stiffness. The chronic ejection into stiff arteries causes the left ventricle to adapt to the higher systolic load by increasing ventricular systolic stiffness and diastolic compliance (Merillon et al. 1985; Chen et al. 1998). This combined ventricular-arterial stiffening ultimately leads to the development of diastolic heart failure (Kass 2005).

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## Systemic Vascular Resistance

In the absence of aortic stenosis and aortic coarctation, systemic vascular resistance is the major determinant of afterload. The three major determinants of systemic vascular resistance are local

vascular regulatory mechanisms (metabolic, myogenic, and endothelial), the autonomic nervous system, and vasoactive peptides.

## Local Vascular Regulatory Mechanisms

The control of local tissue/organ blood flow is regulated by several factors including metabolic factors, myogenic responses, and the endothelial release of relaxing factors (Storkebaum and Carmeliet 2011). The major metabolic controllers of local tissue flow include oxygen, carbon dioxide, adenosine, sodium, and potassium. Tissue hypoxia produces arteriolar vasodilation that is in part mediated by the release of nitric oxide, arachidonic acid metabolites (Roman 2002), and adenosine. The arterial partial pressure of carbon dioxide, through its ability to vasodilate cerebral arterioles, plays an important role in the regulation of cerebral blood flow. In the kidney, distal sodium concentration plays a critical role in renal autoregulation. Renal blood flow and glomerular filtration rate autoregulation are in part due to tubuloglomerular feedback (a special feedback mechanism that links changes in sodium chloride concentration at the macula densa cells in the early distal tubule with control of afferent renal arteriolar resistance; i.e., a decreased delivery of sodium chloride to the macula densa reduces afferent arteriolar resistance which increases glomerular filtration rate) (Braam et al. 1993; Navar et al. 1996).

Myogenic control of blood flow is defined as the ability of blood vessels to constrict in response to increased intravascular pressure independent of neural or humeral influences. This response involves stretch-induced depolarization of vascular smooth muscle cells in high resistance arterioles. With a decrease in intravascular pressure, there is a hyperpolarization of vascular smooth muscle and decrease in vascular resistance. In the kidney, preglomerular arteries and afferent arterioles, but not efferent arterioles, have myogenic responses to changes in wall tension (Navar et al. 1996; Carmines et al. 1990). The myogenic control of the preglomerular arteries and afferent arterioles contributes about half of

the autoregulatory efficiency of the renal vasculature. Chronic hypertension appears to lead to augmented myogenic responses as a result of both structural changes in blood vessels and a change in the intrinsic activation state of the arterioles (Falcone et al. 1993).

The final major mechanism for the local control of regional organ/tissue blood flow and resistance is through the release of endothelial-derived factors (nitric oxide, prostaglandins, and arachidonic acid metabolites). These factors, released by the endothelium, dilate or constrict arterioles. One major mechanism for release of these endothelial-derived factors is vascular shear stress (Koller and Huang 1995). In the kidney, nitric oxide also directly affects tubular sodium transport and appears to be a major mediator of the changes in sodium excretion induced by arterial pressure (Stoos et al. 1995).

### **Autonomic Nervous System Control of Vascular Resistance**

Short- and long-term control of arterial pressure involves the sympathetic and parasympathetic divisions of the autonomic nervous system and the associated neurohormonal systems that are primarily regulated by the hypothalamus and medulla oblongata. Much of the short-term regulation of arterial pressure is accomplished through an intricate and interactive set of feedback mechanisms which include baroreceptors, chemoreceptors, and osmoreceptors.

#### **Baroreceptors**

The brain continuously monitors arterial pressure through stretch-sensitive nerve endings located in the carotid sinuses, aortic arch, cardiac atria, and ventricles. A discussion of the low-pressure (cardiopulmonary) receptors can be found in the pre-load section. The high-pressure (arterial) baroreceptor's afferent pathways consist of axons from the vagal and glossopharyngeal nerves and are transmitted to the nucleus tractus solitarius. The primary function of the high-pressure baroreceptors is for buffering of acute changes in arterial pressure that occur during

normal daily activity. Increases in arterial pressure cause increase in baroreceptor activity which induces reflex parasympathetic activation, sympathetic inhibition, and decreases in heart rate and vascular resistance, whereas decreases in blood pressure decrease baroreceptor activity producing reflex-mediated increases in heart rate and vascular resistance. The baroreflex can also influence secretion of vasopressin and renin (Sladek and Song 2008; Gabrielsen et al. 1996). The baroreceptors can both adapt and reset in response to increases in arterial pressure. Adaptation is the decrease in baroreceptor activity that occurs over a period of seconds to minutes despite the elevated blood pressure and is believed to involve viscoelastic relaxation (Ottesen and Olufsen 2011). In chronic hypertension, the baroreceptors are reset to the higher pressure, and baroreceptor activity returns to near normal levels; however, they are less sensitive, that is, the slope of the arterial pressure-activity curve is decreased (Thrasher 2005a, b). Structural changes in the carotid sinus and aorta that result in decreased compliance are believed to mediate this decrease in baroreceptor sensitivity.

#### **Baroreceptors and Hypertension**

Whether arterial baroreceptors play a role in the pathogenesis of hypertension has been debated for more than 75 years (Thrasher 2005a); however, recent research suggests that the baroreceptors do contribute to the long-term control of blood pressure. Lohmeier et al. (Lohmeier et al. 2003) demonstrated that sustained activation of the central baroreceptors plays an important role in the pathogenesis of obesity hypertension. He and others (Navaneethan et al. 2009; Lohmeier and Iliescu 2011) demonstrated that chronic stimulation of the carotid sinus results in lowering of blood pressure in both experimental obesity hypertension and other types of resistant hypertension. The mechanism for the reduction in blood pressure has been shown to relate to suppression of systemic sympathetic activity, reduction in heart rate, reduction in plasma renin activity, and reduction in glomerular hyperfiltration along with an increase in fractional sodium excretion (Lohmeier et al. 2012).

### **Chemoreceptors and Osmoreceptors**

Receptors in the carotid bodies and adjacent aorta are sensitive to changes in vascular oxygen, carbon dioxide, and hydrogen ion excess. These receptors play a minor role in arterial pressure regulation, except under extreme conditions such as hypoxia, acidosis, or respiratory failure. The osmoreceptors are found in several areas of the brain and periphery (e.g., hepatic osmoreceptors). These receptors influence arterial pressure through regulation of vasopressin secretion (Baertschi et al. 1985).

### **Hypothalamus and Medulla Oblongata and Hypertension**

Although the peripheral autonomic nervous system contributes to certain aspects of blood pressure control, most research suggests that abnormalities at the higher centers of the central nervous system may be critical to the development of hypertension. For example, it has been known for years that the hypertension induced by deoxycorticosterone acetate and high-salt diet in the rat can be eliminated by lesions in the posterior hypothalamus, whereas stimulation in this region intensifies the hypertension (Coruzzi et al. 2005). Similarly, the arcuate nucleus of the hypothalamus has been demonstrated to play a critical role in the pathogenesis of obesity-related hypertension. The arcuate nucleus contains a population of neurons that leads to a decrease in food intake and an increase in energy expenditure, induced in part, via the precursor peptide pro-opiomelanocortin (POMC) (Cowley et al. 2001). Leptin, a 167 amino acid hormone that is secreted exclusively by adipocytes, activates POMC-containing neurons to cause inhibition of food intake and activation of the sympathetic nervous system (Elmquist 2001). An intact pro-opiomelanocortin system is essential for obesity to be associated with high blood pressure. Melanocortin-4 receptor-deficient mice are obese but do not have hypertension, despite hyperleptinemia and hyperinsulinemia (Tallam et al. 2005). In obese melanocortin-4 receptor-deficient humans, Greenfield et al. (Greenfield et al. 2009) demonstrated that the prevalence of hypertension is markedly lower than in obese melanocortin-4 receptor-positive

subjects. In addition, in human obese subjects with functional melanocortin-4 receptors, subcutaneous administration of a melanocortin-4 receptor agonist for 7 days caused significant increases in blood pressure (Greenfield et al. 2009). Sayk et al. (Sayk et al. 2010) demonstrated that in obese subjects with melanocortin-4 receptor mutations, there is an inverse relationship between obesity and muscle sympathetic nerve activity. Finally, Lohmeier et al. (Lohmeier et al. 2003) demonstrated in dogs with obesity-induced hypertension that activation of neurons in the medulla oblongata (nucleus tractus solitarius, caudal ventrolateral medulla, and rostral ventrolateral medulla) is important in the development of hypertension.

### **Vasoactive Peptides**

The release of vasoactive substance is a major way that the body regulates systemic vascular resistance. Other than the catecholamines that are released by either the sympathetic nervous system or adrenal gland, three other important vasoactive agents are renin-angiotensin system (angiotensin II), endothelin, and vasopressin.

### **Renin-Angiotensin System**

Renin is an enzyme that is synthesized, stored, and released by the juxtaglomerular cells of the kidney. It is the rate-limiting enzyme in the biochemical cascade that forms angiotensin II, a potent vasoconstrictor. The physiological regulation of renin release includes the renal baroreceptors, macula densa, and the renal nerves. The renal baroreceptor is a receptor in the afferent glomerular arterioles that stimulates renin production and release when renal perfusion pressure is low and decreases release and production when perfusion pressure is increased. The macula densa, a group of cells in the distal tubule adjacent to the afferent arterioles and juxtaglomerular cells, senses chronic changes in distal tubular sodium delivery. A decrease in sodium delivery leads to an increase in renin production and release. Finally, the renal sympathetic nerves directly innervate the

juxtaglomerular cells, and stimulation of these nerves causes the release of renin. Renin cleaves the decapeptide, angiotensin I (Ang I), from angiotensinogen, and angiotensin I-converting enzyme converts Ang I to angiotensin II (Ang II). Ang II binds to two transmembrane receptors, angiotensin II receptor subtype I (AT<sub>1</sub>) and angiotensin II receptor subtype II (AT<sub>2</sub>), which mediates its physiological actions. Activation of AT<sub>1</sub> results in blood vessel constriction, secretion of aldosterone, amplification of sympathetic nervous system outflow, increased renal sodium retention, and the stimulation of cell growth in the cardiovascular system. Activation of AT<sub>2</sub> opposes the actions of the AT<sub>1</sub> receptor, in that it promotes vasodilation, induces apoptosis, and promotes natriuresis (Johren et al. 2004).

### **Endothelin and the Cardiovascular System**

Endothelin is a potent vasoconstrictor produced by vascular endothelial cells, is released by vascular shear stress (high pressure and low shear stress stimulate release and low pressure and high shear stress inhibit release). Endothelin can be released by Ang II, vasopressin, and catecholamines. Endothelin plays a major physiological role in the local regulation of tissue and organ blood flow; however, its role in the pathophysiology of hypertension is unclear (Schiffriin 2005).

### **Vasopressin and Hypertension**

Vasopressin, or antidiuretic hormone, a peptide that is produced in the posterior pituitary gland in response to reduced cardiopulmonary volume, decreased blood pressure, and increased osmolarity, plays a critical role in salt and water balance but has vasoconstrictor properties. Vasopressin stimulates the distal collecting ducts of the kidney to retain water. It also enhances the sympathoinhibitory influences of the arterial baroreflex and central nervous system, which counter the vasoconstrictor effects of the peptide. As with the endothelins, the role of vasopressin in the pathogenesis of hypertension is unclear (Bakris et al. 1997).

## **Conclusion**

The regulation of the heart and the vasculature are linked by the fundamental principles that the metabolic state of each organ or tissue is dependent on the relationship between metabolism and blood flow and that each organ or tissue has the ability to control its own blood flow according to local metabolic and functional needs. On a whole-body level, these principles are mediated through blood pressure homeostasis (a closed negative feedback loop which regulates mean arterial pressure around a set reference level). Figure 1 schematically depicts that feedback loop for blood pressure homeostasis. An example of how this feedback loop works can be seen in the case of acute blood loss. Acute blood loss results in an acute decrease in preload and a resultant decrease in cardiac output and, at the tissue or organ level, a decrease in nutrient supply, which results in local vasodilation and a resultant slight decrease in systemic vascular resistance. Since both cardiac output and systemic vascular resistance are acutely decreased in such a setting, the net system output (mean arterial pressure) is acutely decreased. Since mean arterial pressure drops below reference levels, the sensors monitoring system output (the central nervous system, the arterial baroreceptors, the atrial stretch receptors and cardiopulmonary baroreceptors, and the renal baroreceptors) feed data back to the controllers (the central nervous system, the sympathetic and parasympathetic nervous system, the renal sympathetic nerves, the kidney (renal pressure-natriuresis curve), and the release of vasoactive substances), which adjust the system (heart and vasculature) to acutely increase cardiac contractility, systemic vascular resistance, and venous return (acute decrease in venous compliance) and chronically increase preload (altering the renal pressure-natriuresis relationship to cause sodium retention) to maintain the desired system output (returning mean arterial pressure to the reference level).

In disease states, the reference level around which arterial pressure is maintained is changed to a new level (e.g., in the case of chronic hypertension the level is increased), and the feedback loop is altered so that controllers (determinant of

blood pressure), the system (heart and vasculature), and the sensors (the physiological monitors of arterial pressure) maintain this new reference level.

## Cross-References

- ▶ [Endothelial Dysfunction and Vascular Remodeling in Hypertension](#)
- ▶ [Insulin Resistance and Other Mechanisms of Obesity Hypertension](#)
- ▶ [Ions and Fluid Dynamics in Hypertension](#)
- ▶ [Neurohumoral and Autonomic Regulation of Blood Pressure](#)
- ▶ [The Role of Dietary Electrolytes and Childhood Blood Pressure Regulation](#)
- ▶ [Vascular and Cardiac Imaging Techniques and Their Applicability to Childhood Hypertension](#)
- ▶ [Vasoactive Factors and Blood Pressure in Children](#)

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**Abstract**

Ion transport is known to be involved in the genesis of hypertension and is utilized therapeutically. However, the mechanisms behind sodium flux that may lead to hypertension are not well understood. Target proteins of diuretic agents, monogenic forms of hypertension, and genetic disorders of renal salt wasting have all provided insight into these pathways. In this chapter, we review some of these channels and their relevance to human hypertension. We explore the role of the cytoskeletal protein adducin in the regulation of sodium transport. We examine the function of the osmotically inactive sodium compartment and its regulation, and hormonal alterations affecting this compartment in salt-sensitive hypertension.

**Keywords**

Sodium channel • Salt sensitive • Adducin • Ouabain • Rostafuroxin • Osmotically active sodium

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**Introduction**

Among the many determinants of blood pressure, ion transport has long been considered important, with its role considered central to the basic understanding and clinical management of hypertension. For decades, clinicians have counseled their hypertensive patients to limit salt intake. Such an approach has been codified in clinical guidelines and forms the backbone of what has been termed therapeutic lifestyle modifications (Chobanian et al. 2003; NHBPEP Working Group on High Blood Pressure in Children and Adolescents 2004; Eckel et al. 2014). Sodium restriction has been studied in clinical trials as an

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effective measure for control of moderately elevated blood pressure (Akita et al. 2003; Obarzanek et al. 2003). In addition to sodium restriction, the role of natriuresis been translated into therapy as thiazide diuretics have assumed the role of first line pharmacologic therapy for hypertension in adults (ALLHAT Investigators 2000, 2003).

At a more basic level, an expanding list of genes has been implicated in monogenic forms of hypertension – genes that typically encode proteins that affect renal tubular sodium handling, reviewed elsewhere in this book (see Part I, “Regulation of Blood Pressure and Pathophysiologic Mechanisms of Hypertension,” ► Chap. 7, “Monogenic and Polygenic Contributions to Hypertension”). Moreover, mutations leading to renal salt wasting, as observed in Bartter and Gitelman syndromes, are associated with normal or low blood pressure.

While monogenic conditions associated with high or low blood pressure provide insight into the pathogenesis of hypertension, these comprise only a small fraction of the overall number of persons with hypertension. More broadly, however, pathogenic changes in ion transport have been implicated in both animal models (see Part V, “Hypertension Research in Pediatrics,” ► Chap. 46, “Hypertensive Models and Their Relevance to Pediatric Hypertension”) and in human studies of essential hypertension, suggesting a role for altered structure and function of ion transporters that provide additional rationale for the success of such measures as salt restriction and diuretics in treating hypertension. In this chapter, we will review some of the ion channels studied in hypertension and their relevance to clinical practice. Both channel function and structure will be considered. We will also discuss alterations in sodium distribution and their impact on blood pressure regulation.

## Sodium Channels

Given the importance of salt in the management of blood pressure, sodium channels have been extensively studied as potential therapeutic targets in

**Table 1** Sodium Transporters along the Renal Tubule

Transporter	Intrarenal location	Cellular location
Na <sup>+</sup> /H <sup>+</sup> exchangers (NHEs)	Proximal tubule and TAL	Apical
Na <sup>+</sup> -K <sup>+</sup> -2Cl <sup>-</sup> cotransporter (NKCC)	TAL	Apical
Epithelial sodium cotransporter (ENaC)	Collecting duct	Apical
Na+Cl <sup>-</sup> cotransporter (NCC)	Distal tubule	Apical
Sodium-potassium ATPase (Na <sup>+</sup> /K <sup>+</sup> ATPase)	Multiple segments	Basolateral

Abbreviations: *TAL* thick ascending limb of the loop of Henle

both animal models of hypertension and in clinical research.

All known relevant channels expressed along the length of the tubule have been studied. These include a variety of sodium transporters – the Na<sup>+</sup>/H<sup>+</sup> exchangers (NHEs), the Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> cotransporter (NKCC), the Na<sup>+</sup>-Cl<sup>-</sup> cotransporter (NCC), as well as the epithelial sodium cotransporter (ENaC) and the sodium-potassium ATPase (Na<sup>+</sup>/K<sup>+</sup> ATPase). See Table 1.

## NHE Transporters

Na<sup>+</sup>/H<sup>+</sup> transporters have been localized throughout the body and play a major role in cell-volume regulation, and the transcellular movement of sodium and osmotically driven water. There are nine NHEs; the NHE1 transporter is ubiquitous, while NHE3 is primarily expressed in the kidney. Both NHE1 and NHE3 have been the focus of much study with respect to hypertension. Specifically, the localization of NHE1 to red blood cells (RBCs) has facilitated its study in humans and in rat models, such as the spontaneous hypertensive rat (SHR).

NHE1 activity is increased in multiple cell types in the SHR, including RBCs, platelets, leukocytes, skeletal muscle, vascular smooth muscle cells, and renal tubular epithelial cells. However,

increased NHE1 activity was not seen in RBCs or proximal tubular cells of a second rat model of essential hypertension, the Milan Hypertensive Strain (MHS). RBC  $\text{Na}^+/\text{H}^+$  transport has been examined in humans as well and appears to correlate with renal sodium retention in hypertensive persons (Diez et al. 1995). The differential effect in SHR versus MHS strains aligns well with human studies, as approximately half of the patients studied had increased RBC  $\text{Na}^+/\text{H}^+$  activity (Canessa et al. 1991; Fortuno et al. 1997). Such increased  $\text{Na}^+/\text{H}^+$  activity likely reflects a systemic effect, as it has also been demonstrated in skeletal muscle in both SHR (Syme et al. 1991) and in humans with essential hypertension (Dudley et al. 1990).

In contrast to NHE1, the NHE3 transporter has a more restricted distribution but does include the proximal tubule, but RBC expression of NHE3 has not been reported. In SHR, NHE3 activity is increased (Hayashi et al. 1997), though mRNA expression is not altered. However, this enhanced activity may be related to decreased expression of the NHE regulatory factor 1 (NHERF1) (Kobayashi et al. 2004), which normally inhibits the activity of NHE transporters, suggesting that NHE3 changes are unrelated to gene expression or structure *per se*. Kelly et al. (1997) studied the relative contributions to sodium transport of NHE1 and NHE3 in proximal tubule cells of SHR. Their studies revealed equal activity of both proteins. While NHE1 protein expression was similar to that of normotensive wild-type controls, NHE3 expression was increased by 50% in SHR. An earlier study (Schultheis et al. 1998) of the NHE3 knockout mouse showed findings of proximal renal tubular acidosis with salt wasting, polyuria, and lower blood pressure, in spite of increases in both renin expression and aldosterone levels. These knockout mice also demonstrated diarrhea, related to absent intestinal expression of NHE3, the other major site of expression.

Human studies of NHE3 in hypertension are limited. Zhu et al. (2004) studied polymorphisms in *SLC9A3* (the gene encoding NHE3) to determine its association with hypertension in an ethnically diverse group of 983 persons, including some with normal and others with elevated blood

pressure. None of six polymorphisms studied was associated with hypertension, although only a subset of the gene sequence was interrogated. Given the small sample size and limited portion of the gene studied, further work is necessary to evaluate the role of *SLC9A3* in predicting human hypertension.

Inhibition of intestinal NHE3 channels has been studied as a therapeutic approach to hypertension. Tenapanor is an NHE3 inhibitor; when administered orally, it acts locally in the intestine to block sodium uptake. In wild-type rats and healthy humans, tenapanor led to an increase in stool sodium and a reduction in urine sodium (Spencer et al. 2014). In rats with chronic kidney disease (CKD) using a 5/6 nephrectomy model, tenapanor prevented the rise in blood pressure and albuminuria seen with the high-salt diet. Rats treated with tenapanor also had lower left ventricular mass relative to vehicle-treated rats, suggesting that control of blood pressure benefited the heart (Spencer et al. 2014). Disappointingly, a small placebo controlled trial of tenapanor in patients with end stage renal disease showed no difference in interdialytic weight gain and pre-dialysis blood pressure (Block et al. 2016). A second study of tenapanor in patients with CKD and Diabetes has not yet been published (Clinicaltrials.gov [NCT01847092] 2013).

## NKCC Transporters

The NKCC family consists of two related proteins, NKCC1 and NKCC2. The first is expressed in a wide variety of tissues, while the second is primarily found in the kidney. In many tissues, both of these channels are activated by shrinkage of cell volume and, conversely, inhibited by cell swelling.

The importance of NKCC2 is related primarily to its role in net sodium and chloride reabsorption in the thick ascending limb of the loop of Henle, and its inhibition by diuretics such as furosemide. This transport system is responsible for approximately 25% of tubular sodium reabsorption. Lifton's group reported that mutations in the gene encoding the NKCC2 protein (*SLC12A1*)

cause type 1 Bartter Syndrome (Simon et al. 1996), a severe form of Bartter Syndrome that has antenatal manifestations with polyhydramnios, prematurity, and postnatal electrolyte wasting and volume depletion. Biochemically, the hallmark of this disease is elevated plasma renin activity and aldosterone level with low to normal blood pressure. Perhaps more clinically relevant are studies by the same group on participants in the Framingham Heart Study, which identified mutations in genes encoding NKCC2, NCCT, and ROMK, which appeared to be protective against hypertension (Ji et al. 2008).

Similar to NHE transporters, the NKCC has also been studied in RBCs in animal models and in humans with hypertension. There is higher activity in RBCs in MHS rats compared to controls, and these animals demonstrate a greater natriuretic response to bumetanide (Salvati et al. 1990). Since this strain has normal expression levels of NKCC2 mRNA and protein (Capasso et al. 2008), it seems unlikely that the increased activity is unrelated to increased gene transcription.

Higher levels of NKCC1 activity have been documented in hypertensive humans, but that finding accounts for only a fraction of patients with low-renin hypertension (Cacciafesta et al. 1994; Cusi et al. 1991, 1993). However, patients with elevated NKCC1 activity also have an exaggerated response to furosemide (Righetti et al. 1995).

## The NCCT

Given the widespread use and success of thiazides in treating essential hypertension, the sparse data on this transporter in both animal models and human hypertension is surprising. Capasso et al. demonstrated increased NCCT mRNA expression in MHS rats, in contrast to NKCC2 and NHE3 mRNA expression, which was not increased (Capasso et al. 2008). Mutations in the *NCCT* gene (*SLC12A3*) were also found to be protective against the development of high blood pressure in Framingham Heart Study participants (Ji et al.

2008). Similarly, heterozygote first-degree relatives of patients with homozygous mutations in *NCCT* (Gitelman Syndrome) had significantly lower blood pressures than controls matched for age, gender, and body mass index (Fava et al. 2008).

## ENaC

Activating mutations in genes encoding the epithelial sodium channel cause Liddle Syndrome, perhaps the best known monogenic form of hypertension. The ENaC is actually a protein complex of three subunits. The regulation of ENaC has been elucidated over the past decade, and includes a complex interaction of intracellular proteins including serum- and glucose-regulated kinase (SGK1) and neural precursor cell expressed, developmentally downregulated 4-2 (Nedd4-2). The putative role of ENaC has also been studied in nongenetic forms of hypertension.

The Dahl salt-sensitive rat strain has been shown to exhibit increased activity of intrarenal ENaC. Specifically, in cell cultures of collecting ducts from these strains, sodium transport was enhanced as compared to control strains and was augmented by aldosterone and dexamethasone (Husted et al. 1996). In follow-up experiments to elucidate whether the effect was due to ENaC or to  $\text{Na}^+/\text{K}^+$  ATPase, sodium transport was unaffected by the  $\text{Na}^+/\text{K}^+$  ATPase inhibitor ouabain, suggesting increased ENaC activity as the cause (Husted et al. 1997).

Liddle Syndrome is caused by mutations in the genes encoding the  $\beta$ - and  $\gamma$ -subunits of ENaC. These mutations result in truncated proteins without the C-terminal end, a segment that is essential for intracellular regulation, and leave ENaC constitutively activated and unaffected by homeostatic stimuli such as aldosterone. Aside from this rare genetic disease, a number of studies have attempted to assess the contribution of ENaC to essential hypertension. Persu et al. studied  $\beta$ -ENaC variants in hypertensive families (Persu et al. 1998). After determining the most

common changes observed in the last exon, they assessed the frequency in a French cohort of 525 patients. Although these changes were seen in only 1% of white persons, the frequency increased up to 44% in those of African ancestry. However, only a fraction of those variants led to changes in sodium flux when studied in *Xenopus* oocytes (Persu et al. 1998).

A relatively common variant in  $\beta$ -ENaC, T594M, has been examined in a number of studies. This variant was first reported by Su et al. (1996) and found in 6% of 231 African American subjects but in none of the 192 Caucasians studied. This variant leads to loss of protein kinase C inhibition, providing a putative mechanism for its effect (Cui et al. 1997). A second study identified an association between this same variant and hypertension in 348 blacks in a study from the UK (Baker et al. 1998). The frequency of this variant was 8.3% among hypertensive persons and 2.1% in those with normal blood pressure. However, a larger study ( $n = 4803$ ) that included a large black population reported no relationship between this variant and hypertension (Hollier et al. 2006). Moreover, administration of amiloride to those with this variant did not demonstrate any differential effect as compared to those with wild-type  $\beta$ -ENaC. Thus, the role of ENaC variants in essential hypertension remains to be fully elucidated.

### **Na<sup>+</sup>/K<sup>+</sup> ATPase**

The ubiquitous Na<sup>+</sup>/K<sup>+</sup> ATPase solute pump generates the driving force for a myriad of transport processes. In the renal tubule, the pump results in net sodium gain, facilitating epithelial sodium reabsorption along the length of the renal tubule. Earlier studies revealed increased Na<sup>+</sup>/K<sup>+</sup> ATPase activity in MHS kidney extracts as compared with controls (Melzi et al. 1989). This phenomenon was due to increased activity of the pump *per se*, since pump number was not increased, as assessed by the number of ouabain-binding sites (Parenti et al. 1991).

In contrast to primary overactivity of this pump, Blaustein et al. (2009) proposed an alternative model, based on an unidentified endogenous ouabain-like substance. They hypothesized that salt retention leads to production of this ouabain-like substance, which then increases vasomotor tone due to the linked effects of the Na<sup>+</sup>/K<sup>+</sup> ATPase and calcium flux (Hauptert 1988). While acute administration of ouabain to rats may induce protective effects, such as increased generation of nitric oxide in response to acetylcholine, chronic administration in the rat model induces hypertension that blunts the effects of acetylcholine and generates endothelial dysfunction (Cao et al. 2009). An endogenous ouabain-like substance has been isolated from MHS and mammalian hypothalamus (Murrell et al. 2005).

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### **Calcium Flux**

Sodium and calcium flux are interrelated, most notably due to the effects of the Na<sup>+</sup>/K<sup>+</sup> ATPase and crosstalk with the Na<sup>+</sup>/Ca<sup>2+</sup> exchanger (NCX). This effect has been harnessed therapeutically with the use of digoxin to increase myocardial contractility. Inhibition of the Na<sup>+</sup>/K<sup>+</sup> ATPase leads to an increase in intracellular sodium levels with secondary redistribution of calcium due to NCX (Blaustein 1993). The resulting rise in intracellular calcium improves contractility in cardiac myocytes and vascular smooth muscle cells (VSMCs). This link has been further established on a cellular compartment level with colocalization of Na<sup>+</sup>/K<sup>+</sup> ATPase and NCX.

It should be noted that differing Na<sup>+</sup>/K<sup>+</sup> ATPase subtypes likely mediate this effect, with the  $\alpha 2$  subtype having the greatest affinity for endogenous ouabain and its effect on VSMCs (Ferrandi et al. 1992; Tao et al. 1997). In mice, expression of the  $\alpha 2$  subtype with a shortened N-terminus is dominant negative for expression of wild-type full length  $\alpha 2$  pumps (Song et al. 2006). When this dominant negative  $\alpha 2$  pump was expressed using a smooth muscle-specific myosin promoter, reduced pump function and

elevated blood pressure were observed (Blaustein et al. 2009). Conversely, mice that overexpress the  $\alpha 2$  pump within smooth muscle have significantly lower blood pressure than  $\alpha 2$  wild-type mice and mice with  $\alpha 1$  overexpression (Pritchard et al. 2007).

The relation between these transporters suggests a sequence by which increased salt and water intake leads to volume expansion, followed by secondary release of endogenous ouabain (Blaustein et al. 2009; Hamlyn et al. 1996). The inhibition of the  $\text{Na}^+/\text{K}^+$  ATPase attempts to prevent further sodium retention by the kidneys. However, within VSMCs, this effect enhances calcium uptake via NCX with a resultant increase in intracellular calcium and vasoconstriction. Furthermore, because of membrane depolarization related to  $\text{Na}^+/\text{K}^+$  ATPase inhibition, L-type calcium channels would be activated leading to further calcium influx, resulting in a net increase in vascular tone.

The effects of ouabain on the  $\alpha 2$  pump subtype as described above lead to increased vascular tone. However, the  $\alpha 1$  pump found in the renal tubular epithelium leads to net sodium retention and would theoretically be inhibited by ouabain. This discordance can be explained by the differential effects of physiological levels of ouabain on the different pump isoforms. As noted, ouabain inhibits the  $\alpha 2$  pump, leading to calcium influx into VSMCs and increased vascular tone. In contrast, ouabain may have a net stimulatory effect in the kidney at the  $\alpha 1$  pump via stimulation of epidermal growth factor receptor and subsequent phosphorylation and activation of the  $\alpha 1$  pump (Haas et al. 2000; Liu et al. 2000). Thus the differential effect on isoforms of the  $\text{Na}^+/\text{K}^+$  ATPase leads to a net increase in blood pressure (Ferrari et al. 2006).

Perhaps the most exciting outgrowth of this research is the development of an inhibitor of the  $\text{Na}^+/\text{K}^+$  ATPase for the treatment of hypertension. Rostafuroxin (PST 2238) is a steroid compound that competitively binds to  $\text{Na}^+/\text{K}^+$  ATPase and inhibits the effects of ouabain. In MHS rats, rostafuroxin lowered blood pressure compared to vehicle. This effect was also seen in control rats treated with ouabain, deoxycorticosterone acetate,

and salt-treated rats in a remnant kidney model (Ferrari et al. 1999, 2006). A recent phase II clinical study in hypertensive patients showed no effect of five different doses on blood pressure lowering (Staessen et al. 2011). However, when stratified by genotype, rostafuroxin showed a significant drop in blood pressure (Lanzani et al. 2010). Patients with variants in genes encoding enzymes for ouabain synthesis, ouabain transport, and the cytoskeletal protein adducin responded to all doses of rostafuroxin, in contrast to patients receiving losartan, hydrochlorothiazide, or placebo.

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### Regulation of Ion Flux: The Role of $\alpha$ -Adducin

While multiple channels have increased activity that leads to net sodium reabsorption and hypertension in both animal and human studies, the exact mechanism of this regulation remains unclear. The transporters studied generally do not have increased levels of mRNA or protein, and the association studies for specific polymorphisms in these models have provided conflicting data. However, the cytoskeleton has been implicated as having a role in this altered functional activity. Adducin, which is a heterodimeric cytoskeleton protein, which has an alpha subunit plus either a beta or gamma subunit, is ubiquitously expressed. Adducin is found in both rats and humans, and its association with salt-sensitive hypertension has been described in both.

Adducin mutations in both  $\alpha$ - and  $\beta$ -subunits have been associated with hypertension in MHS rats (Bianchi et al. 1994), leading to increased  $\text{Na}^+/\text{K}^+$  ATPase activity in renal tubular epithelium (Tripodi et al. 1996). This group later described that MHS rats with these mutations did not have the expected endocytosis of  $\text{Na}^+/\text{K}^+$  pumps in response to dopamine (Efendiev et al. 2004) which may reflect a broader alteration in clathrin-dependent endocytosis (Torielli et al. 2008). Other groups have shown that in a variety of rat models of hypertension, genes encoding adducin subunits have been found within quantitative trait loci for hypertension

(Orlov et al. 1999). As described above, rostaduroxin reduces blood pressure in hypertensive MHS rats (Ferrari et al. 1999, 2006) and humans (Lanzani et al. 2010) with adducin mutations.

$\alpha$ -Adducin polymorphisms have been described in salt-sensitive human hypertension as well. In an Italian study of 936 persons, including hypertensive siblings, hypertensive individuals, and normotensive controls, the G460W polymorphism was studied, with a significant association seen in this population (Cusi et al. 1997). Interestingly, this relationship was not seen in a cohort of 375 Scottish patients (Kamitani et al. 1998) or 507 Japanese patients (Kato et al. 1998). A meta-analysis of the G460W in Chinese Han population found an association between this polymorphism and essential hypertension (Li 2012). The role of  $\alpha$ -adducin polymorphisms in hypertension will require further elucidation, especially given the antihypertensive effects of rostaduroxin in this population.

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## Sodium Distribution and Blood Pressure

An additional factor in the salt-mediated regulation of blood pressure is the distribution of sodium itself. Sodium intake leads to volume expansion, but distribution to other body compartments exists to offset this effect in rise in blood pressure. *Osmotically active sodium* refers to the changes seen in total body water with sodium intake. In contrast, *osmotically inactive sodium* describes sodium distribution that does not alter volume and may protect against sodium-induced changes in blood pressure.

This concept was studied in the Dahl salt-sensitive (SS) rat strain (Titze et al. 2002). Compared to the Dahl salt resistant strain and the Sprague Dawley (SD) rats, when fed a high-salt diet, SS rats had an expected increase in total body water, total body salt, and blood pressure. To study the osmotically inactive sodium compartment, bone sodium content was investigated. The SS strain showed an increase in bone sodium content, but the bone sodium to total body sodium

ratio (Bone Na/TBS) actually dropped in these animals compared to the other strains. This ratio was also inversely correlated with total body water and blood pressure in the SS rats, while no relationship was seen in other strains. Thus, in the SS rats the osmotically inactive bone sodium compartment was inadequate to handle the high-salt diet and contributed to the development of hypertension (see also Part I, “Regulation of Blood Pressure and Pathophysiologic Mechanisms of Hypertension,” ► Chap. 10, “The Role of Dietary Electrolytes and Childhood Blood Pressure Regulation”).

These investigators later studied the role of skin in SD rats as a compartment for osmotically inactive sodium (Titze et al. 2003). Ovariectomized rats were compared to male and fertile female SD rats based on observation of differential salt sensitivity in females compared to males. While all groups showed an increase in skin sodium after a high-salt diet, the ovariectomized rats showed a smaller increase. Similarly, the ratio of skin sodium to total body sodium did not change in ovariectomized rats while it rose in fertile female and male rats. In contrast, the Dahl strains showed no change in skin sodium content. They later demonstrated that this osmotically inactive sodium storage was related to increased skin glycosaminoglycan (GAG) content, and that genes regulating GAG expression could be actively induced by salt loading (Titze et al. 2004). The regulation of sodium in this compartment may be further connected to hormonal mechanisms within local macrophages (Machnik et al. 2009). In this study, high salt intake in SD rats led to expression of the angiogenic factor Vascular Endothelial Growth Factor-C (VEGF-C) and increased lymphatic channel production, as well as greater skin GAG content. Depletion of macrophages blunted this effect and exacerbated the hypertension of salt loading in these rats with extracellular volume expansion.

The relation between skin sodium content and blood pressure has been studied in humans. Using  $^{23}\text{Na}$  MRI, sodium content was measured in skin and muscle in a cohort of hypertensive and normotensive individuals (Kopp et al. 2013). Skin sodium content increased in parallel with age

and blood pressure. In the same study, humans with refractory hypertension also had higher skin and muscle sodium. Spironolactone treatment led to both an improvement in blood pressure and decrease in muscle sodium content.

The role of VEGF-C in salt-sensitive hypertension has also been studied in humans. In a cohort of adults with mild chronic kidney disease and proteinuria, a high-salt diet was associated with a rise in VEGF-C levels and blood pressure (Slagman et al. 2012). In healthy individuals, the rise in VEGF-C did not achieve statistical significance ( $p = 0.07$ ), and blood pressure was unchanged. Extracellular volume and NT-proBNP levels followed a similar pattern in both groups. The investigators conclude that VEGF-C may serve as a marker of salt-sensitive hypertension (see also Part I, “Regulation of Blood Pressure and Pathophysiologic Mechanisms of Hypertension,” ► Chap. 12, “Stress and Salt Sensitivity in Childhood Hypertension”).

They further investigated the role of VEGF-C using sunitinib, a tyrosine kinase inhibitor that blocks VEGF receptor signaling and causes hypertension as a side effect of therapy in humans (Lankhorst et al. 2015). WKY rats were fed normal and high-salt diets, both before and after sunitinib administration. BP rose both with a high-salt diet and with sunitinib, and the combination led to an even greater increase. Skin sodium rose with high-salt diet and further with the combination. Skin sodium content correlated with BP rise.

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## Conclusions

Aberrant ion transport is a critical component in the pathogenesis of hypertension. The research presented here reflects only a subset of the published data in this field. It also represents an exciting area of potential study in children and adolescents with essential hypertension, many of whom are salt sensitive. The role of rosfuroxin remains to be established in the treatment of hypertension, but establishes a new class of agent that more directly targets essential

hypertension without the complicating metabolic side effects of thiazides. The role of adducin mutations and polymorphisms has yet to be investigated in pediatric hypertension and presents an untapped avenue for further investigation.

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## Cross-References

- [Hypertensive Models and Their Relevance to Pediatric Hypertension](#)
- [Monogenic and Polygenic Contributions to Hypertension](#)
- [Stress and Salt Sensitivity in Childhood Hypertension](#)
- [The Role of Dietary Electrolytes and Childhood Blood Pressure Regulation](#)

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# Uric Acid in the Pathogenesis of Hypertension

Daniel I. Feig

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## Abstract

Over the last century uric acid has been considered a possible risk factor for hypertension, cardiovascular disease, and kidney disease. Only in the last 15 years, however, have there been animal models and clinical trials to support a truly mechanistic link. Results from animal models suggest a two-phase mechanism for the development of hyperuricemic hypertension, in which uric acid induces acute vasoconstriction by activation of the renin-angiotensin system, followed by enhanced uric acid uptake into vascular smooth muscle cells leading to cellular proliferation and secondary arteriosclerosis that impairs pressure natriuresis. The acute phase of hypertension in that model remains uric acid dependent and sodium independent, whereas the chronic hypertension in experimental models becomes uric acid independent and sodium dependent. Small clinical trials, performed in adolescents with newly diagnosed essential hypertension, demonstrate that reduction of plasma uric acid can reduce blood pressure. Small clinical trials in older adults and persons with chronic renal disease have demonstrated less response to urate lowering therapy, consistent with the two-step model. The

available data suggest that uric acid, given its apparent role in the pathogenesis of hypertension, may be a viable target for treatment or prevention in some cases of early onset hypertension.

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## Keywords

Uric acid • Hypertension • Fructose • Children • Obesity • Metabolic syndrome • Cardiovascular disease • Clinical trials

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## Introduction

The possibility that uric acid may be involved in the pathogenesis of hypertension has been considered for more than a century. Frederick Mahomed, in the 1870s, postulated that hypertension resulted from a circulating toxin that caused an increase in blood pressure and subsequently damaged the

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vasculature of the heart and kidneys (Mahomed 1879). While he suggested several candidate molecules, he proposed **uric acid** as an important mediator when he published the first sphygmograph tracings from a patient with gout and increased systemic blood pressure (Mahomed 1879). A few years later Alexander Haig also linked uric acid with elevated blood pressure and wrote a textbook that suggested that diet to lower uric acid might control blood pressure in the general population (Haig 1897). In 1897 Nathan Davis, in an address to the American Medical Association, proposed that **gout** was a major cause of hypertension that manifested as arteriolar disease, interstitial renal injury, and myocardial hypertrophy (Davis 1897). In 1909, Henri Huchard hypothesized that the vascular lesions associated with hypertension had three causes – uric acid, lead, and intake of fatty meats, the last of which also yield increased uric acid (Huchard 1909). In 1913 Desgrez reported the first animal model evidence to support a link between uric acid and hypertension, noting that uric acid infusions increased blood pressure in a rabbit model (Desgrez 1913). In 1915 urodonal, a combination drug consisting of theobromine and methenamine, was introduced in France as a treatment to lower uric acid and control blood pressure; however, it was eventually proven ineffective. Nevertheless, by the end of the nineteenth century and the first two decades of the twentieth century, uric acid was considered as having a putative link with hypertension and cardiovascular diseases.

Interest in the possible link between hypertension and uric acid waxed and waned during much of the twentieth century, though it has dramatically increased over the last 30 years. While some cardiovascular risk trials measured uric acid and suggested an association between uric acid and hypertension, or cardiovascular disease, two factors led most investigators to conclude that uric acid was an associated surrogate marker for more important risk factors such as obesity, diabetes, and **chronic kidney disease (CKD)** (Culleton et al. 1999). The first was a lack of a plausible physiological mechanism and the second was that despite consistent correlation, the link between plasma uric

acid and cardiovascular disease was not always statistically independent of hypertension, renal disease, and diabetes. In the 1980s, uric acid was removed from some of the common laboratory panels, markedly reducing the availability of epidemiologic data on uric acid both in apparently well patients and in those suffering from cardiovascular disease. Removing uric acid from lab panels was done because the majority of serious side effects from **allopurinol**, used to decrease urate levels, were observed in patients with asymptomatic hyperuricemia (Gutierrez-Macias et al. 2005). Thus, obtaining fewer routine determinations of uric acid would mean that fewer asymptomatic patients would be detected and then placed on allopurinol with its attendant side effects.

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### Animal Models of Hyperuricemic Hypertension

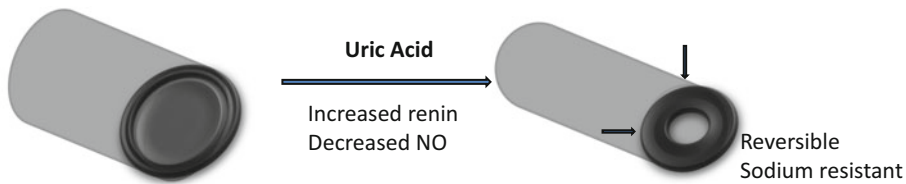
While substantial epidemiological evidence supported the hypothesis that uric acid may be associated with hypertension, it was not until the experiments of Johnson and colleagues in 2001 (Mazzali et al. 2001) established a plausible mechanism that uric acid received greater attention (Table 1). Using a rat model of pharmacologically induced hyperuricemia, they found that increased plasma uric acid results in hypertension within 2 weeks, with increases in SBP and DBP proportional to those of uric acid. The urate-induced experimental hypertension can be ameliorated by uric acid lowering drugs (allopurinol or benzydaronone). While early hypertension in this model is completely reversible with urate reduction, prolonged hyperuricemia results in irreversible sodium sensitive hypertension that becomes uric acid independent (Mazzali et al. 2001, 2002). The early hypertension in this model is mediated, at least in part, by increased renal renin release, as well as reduction of circulating plasma nitrates (Gersch et al. 2007; Mazzali et al. 2001; Sanchez-Lozada et al. 2007; Sautin et al. 2007), leading to a phenotype of excessive vasoconstriction that can be reversed by reduction of uric acid or

**Table 1** Animal model data suggest roles for uric acid in hypertension

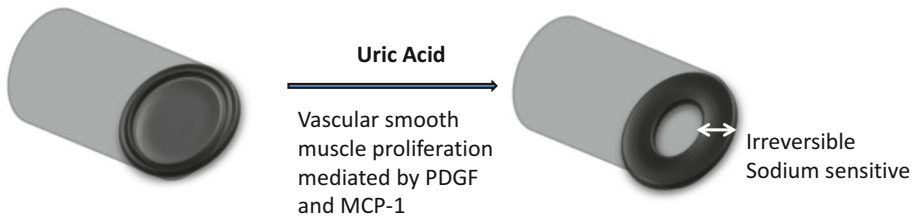
Uric acid effect	System	Specific observations	Reference
Causes hypertension in rats	Rats fed uricase inhibitor	Hyperuricemia results in hypertension within 2 weeks. SBP and DBP are proportional to plasma uric acid. Hypertension is ameliorated by uric acid lowering drugs (allopurinol or benzydaron). Prolonged hyperuricemia results in irreversible sodium sensitive hypertension.	Mazzali et al. (2001), Mazzali et al. (2002)
Causes endothelial dysfunction in rats	Rats fed uricase inhibitor	Hyperuricemic rats have lower plasma nitrates than controls. Treatment with L-arginine corrects the hypertension and increases urinary nitrites. The mechanism likely results from stimulation of arginase and by direct reaction of NO to form aminouracil.	Gersch et al. (2007), Mazzali et al. (2001), Sanchez-Lozada et al. (2007), Sautin et al. (2007), Zharikov et al. (2008)
Activates RAS in rats	Rats fed uricase inhibitor	Renal renin is increased in hyperuricemic rats, and lowering uric acid reduced renin expression and corrected BP. Urate infusion caused rapid renin release via a COX-2 and macula densa dependent mechanism.	Mazzali et al. (2002), Toma et al. (2007)
Causes arteriosclerosis in rats	Rats fed uricase inhibitor	Hyperuricemia induces renal microvascular injury resulting in renal ischemia, intrarenal inflammatory cell infiltration, intrarenal oxidative stress, and the development of hypertension.	Cirillo et al. (2009), Johnson et al. (2002), Johnson et al. (2005), Kanellis et al. (2003), Rodriguez-Iturbe et al. (2004), Roncal et al. (2007)
Exacerbates progressive renal injury in rats	Rats fed uricase inhibitor	Hyperuricemic rats develop spontaneous renal disease, with progressive glomerulosclerosis and tubulointerstitial fibrosis. Hyperuricemia exacerbates, glomerulosclerosis and GFR decline in 5/6 nephrectomy and cyclosporin nephrotoxicity models.	Kang et al. (2002)
Causes metabolic syndrome in rats	Rats fed uricase inhibitor	High fructose diet results in hyperuricemia, weight gain hyperinsulinemia, and hypertriglyceridemia within 4 weeks. This was mitigated by uric acid lowering agents.	Nakagawa et al. (2006)
Causes endothelial cell dysfunction in vitro	Primary endothelial cell culture	Uric acid inhibits NO production by HUVEC cells and decreases cell proliferation and migration. Mechanisms include induction of arginase, scavenging NO, and formation of aminouracil.	Gersch et al. (2007), Kang et al. (2005), Sautin et al. (2007), Zharikov et al. (2008)
Causes vascular smooth muscle cells proliferation	Primary vascular smooth muscle cell culture	Uric acid enters cells via URAT resulting in activation of MAP kinases, COX-2 generation, and the production of growth factors (PDGF) and inflammatory proteins (CRP, MCP-1).	Kanellis et al. (2003), Kang and Johnson (2003), Kang et al. (2002), Price et al. (2006), Watanabe et al. (2002)
Impaired adipocyte function	Adipocyte tissue culture	Uric acid downregulates PPAR $\gamma$ and adiponectin.	Sautin et al. (2007)

Abbreviations: COX-2, cyclooxygenase-2; GFR, glomerular filtration rate; NO, nitric oxide; HUVEC, human umbilical vein endothelial cells; URAT, uric acid anion transporter-1; MAP kinase, mitogen activated protein kinase; PDGF, platelet derived growth factor; CRP, c reactive protein; MCP-1, monocyte chemoattractant protein-1

### Phase 1: Acute Vasoconstriction



### Phase 2: Arteriolar Wall Hypertrophy



**Fig. 1** Data from animal models suggest that hyperuricemia leads to hypertension in a stepwise fashion. The effects of uric acid on the blood vessel are shown. The first phase is direct, uric acid-dependent activation of the renin-angiotensin system and downregulation of the nitric oxide production, leading to vasoconstriction. At this stage, uric acid reduction results in vascular relaxation and improved blood pressure. The second phase, which develops over time, is uric acid-mediated arteriosclerosis. Uric acid

uptake into vascular smooth muscle cells leads to the activation and elaboration of PDGF and MCP-1, resulting in the autocrine stimulation of vascular smooth muscle cell proliferation, resulting in vascular wall thickening without vasoconstriction, loss of vascular compliance, and a shift in pressure natriuresis. This second phase is not reversed by the late reduction of uric acid and thus causes permanent sodium sensitive hypertension

by renin-angiotensin system blockade. Later, the hypertension is irreversible, secondary to altered intrarenal vascular architecture. Uric acid enters **vascular smooth muscle cells (VSMC)** via **URAT1** channel, resulting in activation of kinases, nuclear transcription factors, cyclooxygenase-2 (COX-2) generation, and the production of growth factors (PDGF) and inflammatory proteins (e.g., C reactive protein, monocyte chemoattractant protein-1) resulting in the VSMC proliferation, shifted pressure natriuresis, and sodium sensitive hypertension (Kanellis et al. 2003; Kang and Johnson 2003; Kang et al. 2002; Price et al. 2006; Watanabe et al. 2002) (see Fig. 1). If recapitulated in humans, this model would imply that there may be an early period of reversible hyperuricemic hypertension before sustained hypertension develops.

These mechanistic studies, as well as the recent epidemiologic data described below, have led to further investigation that addresses the link between uric acid and hypertension.

## Epidemiology

Numerous longitudinal cardiovascular risk trials have evaluated the possible relation between plasma uric acid, hypertension, cardiovascular disease, and chronic kidney disease (see Tables 2, 3, and 4). As early as 1972, the Israeli Heart Trial, an evaluation of the medical data of young armed services inductees, demonstrated that the highest tertile of uric acid was associated with double the risk of incident hypertension within 5 years of that baseline measurement (Kahn et al. 1972). The association appears to be robust across racial groups with similar findings in African Americans noted in the CARDIA trial (Dyer et al. 1999), as well as in several trials demonstrating the same association in Asians and Asian Americans (Imazu et al. 2001; Masuo et al. 2003; Nagahama et al. 2004; Nakanishi et al. 2003; Taniguchi et al. 2001). Several studies in children and adolescents, particularly the Hungarian Children's

**Table 2** Epidemiology of uric acid and hypertension

Study	Population	Risk of hypertension	Reference
Israeli Heart (1972)	10,000 Israeli men, age 17–25 enrolled at military induction	2-fold risk at 5 years	Kahn et al. (1972)
Fessel (1973)	224 white males in Western USA, age > 35 years	Greater increase in SBP at 4 years	Fessel et al. (1973)
Gruskin (1985)	55 adolescents, racially mixed US population	Higher uric acid, higher BP	Gruskin (1985)
Brand (1986)	4286 men and women age 35–50 in the Framingham cohort	Uric acid, SBP rise a linear relation	Brand et al. (1985)
Hungarian Children's (1990)	17,643 Hungarian children, age 6–19	Uric acid predicts adolescent hypertension	Török et al. (1985)
Kaiser Permanente (1990)	2062 adult men and women in the Kaiser Permanente Multiphasic Health Checkup cohort in Northern California	2-fold risk at 6 years	Selby et al. (1990)
University of Utah (1991)	1482 adult men and women in 98 Utah pedigrees	2-fold risk at 7 years	Hunt et al. (1991)
NHANES (1993)	6768 healthy children age 6–17	Uric acid predicts adolescent hypertension	Goldstein and Manowitz (1993)
Olivetti Heart Study (1994)	619 adult males from Southern Italy	2-fold risk at 12 years	Jossa et al. (1994)
CARDIA Study (1999)	5115 black men and women age 18–30	Increased risk at 10 years	Dyer et al. (1999)
Osaka Health Survey (2001)	6356 Japanese men age 35–60	2-fold risk at 10 years	Taniguchi et al. (2001)
Hawaii-LA-Hiroshima Study (2001)	140 Japanese American males age 40–69	3.5-fold risk at 15 years	Imazu et al. (2001)
Feig and Johnson (2003)	175 racially diverse children, age 6–18 in Texas	Uric acid >5.5 mg/dL predicts hypertension	Feig and Johnson (2003)
Osaka Factory Study (2003)	433 nonobese Japanese men age 18–40	1.0 mg/dl ↑27 mmHg SBP at 5 years	Masuo et al. (2003)
Osaka Health Survey (2003)	2310 male office workers in Japan, age 35–59	1.6-fold risk at 6 years	Nakanishi et al. (2003)
Okinawa (2004)	4489 Japanese men and women, age > 30	1.7-fold risk at 13 years	Nagahama et al. (2004)
Bogalusa Heart (2005)	577 black (58%) and white (42%) children enrolled at age followed until age 18–35	↑ risk for diastolic HTN at 11 years	Alper et al. (2005)
Framingham (2005)	3329 men and women in the Framingham cohort	1.6-fold at 4 years	Sundstrom et al. (2005)
Normative Aging Study (2006)	2062 healthy men age 40–60 at enrollment	1.5-fold at 21 years	Perlstein et al. (2006)
ARIC (2006)	9104 mixed race (black and white) men and women age 45–64 years at enrollment	1.5-fold at 9 years	Mellen et al. (2006)
Beaver Dam Survey (2006)	2520 White men (44%) and women (56%) age 43–84 in Wisconsin	1.65-fold at 10 years	Shankar et al. (2006)
Health Professional Follow-up (2006)	750, mostly white men in Massachusetts	1.08-fold at 8 years	Forman et al. (2007)

(continued)



**Table 2** (continued)

Study	Population	Risk of hypertension	Reference
MRFIT (2007)	3073 men age 35–57 years	1.8-fold at 6 years	Krishnan et al. (2007)
Nurses Health (2009)	1496 women, racially diverse, age 32–52	1.9-fold at 6 years	Forman et al. (2009)
Qingdao Port Health (2009)	7220 men (74%) and women (26%) in Qingdao, China, mean age 37	1.39 for men, 1.85 for women at 4 years	Zhang et al. (2009)
Jones (2009)	141 children age 7–18, 64% male, 71% black	2.1-fold risk in adolescence by ABPM	Jones et al. (2009)
Leite (2010)	1410 men and women in Milan, Italy, young cohort 42–59 years, older cohort 60–74	Increased risk in middle age, not elderly	Leite (2011)
Grayson (2010)	55,607 adults, meta-analysis of 18 prospective studies	1.41-fold risk each 1 mg/dL uric acid	Grayson et al. (2011)
Silverstein (2011)	108 racially diverse children, age 6–18 in Texas and Washington, DC	linear association between SBP and uric acid in children on renal replacement therapy	Silverstein et al. (2011)
GOCADAN (2012)	1078 Alaskan Native Americans with CKD II-III	1.2-fold age adjusted risk	Jolly et al. (2012)
Fadrowski (2012)	6036 adolescents, age 11–17 evaluated in NHANES	Uric acid >5.5 mg/dL, 2.03-fold risk	Loeffler et al. (2012)
Yokoi (2016)	26,442 Japanese males age 18–60	1.48-fold risk in highest tertile of uric acid	Yokoi et al. (2016)

**Table 3** Epidemiology of uric acid and cardiovascular disease

Study	Population	CV Risk	Reference
Lehto (1998)	1017 diabetics, mean age 58 years, followed for 7 years	OR 1.91, independent on MR	Lehto et al. (1998)
Liese (1999)	1044 healthy adults, 50–60 year, followed for 8 years	OR 1.7–2.8, independent on MR	Liese et al. (1999)
Alderman (1999)	7978 hypertensive adults, mean age 53, followed for 6 years	OR 1.5, independent on MR	Alderman et al. (1999)
Fang (2000)	5926 healthy adults, mean age 48, followed for 16 years	OR 3.0, independent on MR	Fang and Alderman (2000)
Franse (2000)	4327 elderly adults, mean age 71, followed for 5 years	OR 1.5, independent on MR	Franse et al. (2000)
Verdecchia (2000)	1720 adults with hypertension, mean age 51, followed for 4 years	OR 1.9, independent on MR	Verdecchia et al. (2000)
Mazza (2001)	3282 healthy adults, mean age 74, followed for 14 years	OR 1.6, independent on MR	Mazza et al. (2001)
Wang (2001)	1873 Chinese adults mean age 66, followed for 3 years	OR 1.34, independent on MR	Wang et al. (2001)

(continued)

**Table 3** (continued)

Study	Population	CV Risk	Reference
Bickel (2002)	1017 with coronary artery disease, mean age 62, followed for 2.2 years	OR 2.7, independent on MR	Bickel et al. (2002)
Weir (2003)	2482 stroke patients, mean age 72, follow-up 2 years	OR 1.3, independent on MR	(Weir et al. 2003)
Niskanen (2004)	1423 healthy Finnish adults, mean age 53, followed for 12 years	OR 4.8, independent on MR	Niskanen et al. (2004)
Athyros (2004)	1600 adults with hypertension and congestive heart failure, mean age 59, followed for 3 years	OR 3.0, independent on MR	Daskalopoulou et al. (2004)
Hakoda (2005)	10,615 atomic bomb survivors, mean age 49, followed for 25 years	OR 1.8, independent on MR	Hakoda et al. (2005)
Suliman (2006)	294 adults with ESRD, mean age 53, followed for 3 years	OR 1.3, independent on MR	Suliman et al. (2006)
Bos (2006)	4385 adults in Rotterdam Study, above age 55, followed for 8.5 years	OR 1.7, independent on MR	Bos et al. (2006)
Culleton (1999)	6763 adult men, mean age 47, followed for 4 years, Framingham cohort	OR 4.1, not independent on MR	Culleton et al. (1999)
Moriarity (2000)	13,504 healthy adults, mean age 50, followed for 8 years	OR 3.0, not independent on MR	Moriarity et al. (2000)
Sakata (2001)	8172 healthy adults, mean age 49, followed for 14 years	OR 2.3, not independent on MR	Sakata et al. (2001)
Simon (2006)	2763 women, mean age 66, followed for 4 years	OR 1.1, not independent on MR	Simon (2006)
Xia (2016)	25,453 patients with CKD, meta-analysis	HR 1.52 for CV mortality	Xia et al. (2016)

Study (Török et al. 1985), the Moscow Children's Study (Rovda Iu 1992), and the National Health And Nutrition Examination Survey (NHANES) (Goldstein and Manowitz 1993), in the 1980s and early 1990s, demonstrated a particularly strong association between uric acid and hypertension. Studies in older and elderly patients have had more variable results (Culleton et al. 1999; Nefzger et al. 1973; Saito et al. 2000; Staessen 1991). In particular, some of those studies found that the association between uric acid and cardiovascular (CV) risk did not remain significant using multiple regression models, particularly if the risk conferred by hypertension is controlled in

the model (Culleton et al. 1999; Moriarity et al. 2000; Sakata et al. 2001; Simon 2006). One explanation may be that the CV risk caused by uric acid functions through the development of hypertension but not after it is fully developed; alternatively, high uric acid in the young may have a relatively greater effect.

In the past decade new epidemiological studies have rekindled an interest in the link between uric acid and hypertension. Three longitudinal Japanese studies showed an association between plasma uric acid and incident hypertension. Nakanishi et al. demonstrated a 1.6-fold increased risk of new hypertension over 6 years in young

**Table 4** Uric acid and chronic kidney disease

Study	Population	Major findings	Reference
Iseki (2001)	6403, Okinawa General Health	Uric acid >8 mg/dl increase CKD risk 3-fold in men and 10-fold in women	Iseki et al. (2001)
Siu (2006)	54 middle aged men, nonrandomized treatment trial	CKD patients with mean uric acid 9.75 mg/dL treated with 100–300 mg/day allopurinol, possible slower progression	Siu et al. (2006)
Chonchol (2007)	5808, Cardiovascular Health Study	Uric acid strongly associated with prevalent but weakly with incident CKD	Chonchol et al. (2007)
Kanbay (2007)	59 subjects, randomized to treatment with allopurinol	Hyperuricemic patients treated with allopurinol had increased GFR, whereas patients with normal uric acid did not	Kanbay et al. (2007)
Obermayr (2008)	21,457 Vienna Health Screening Project	Uric acid >7 mg/dL increased risk of CKD 1.74-fold in men, 3.12-fold in women	Obermayr et al. (2008)
Sturm (2008)	227, Mild to Moderate Kidney Disease (MMKD) Study	Uric acid predicted progression of CKD only in unadjusted sample	Sturm et al. (2008)
Weiner (2008)	13,338, Atherosclerosis Risk in Communities (ARIC)	Each 1 mg/dL increase in uric acid increase risk of CKD 7–11%	Weiner et al. (2008)
Borges (2009)	385 adult women	Elevated uric acid associated with 2.63-fold increased risk of CKD in hypertensive women	Borges et al. (2009)
Chen N (2009)	2596, Ruijin Hospital, China	Linear correlation between uric acid and degree of CKD	Chen et al. (2009a)
Chen Y (2009)	5722, Taipei University Hospital	Uric acid associated with prevalent CKD in elderly	Chen et al. (2009b)
Foley (2007)	15,837 patients in NHANES III Cohort	Minority patients with higher uric acid had increased risk of GFR decline	Foley et al. (2007)
Madero (2009)	840, Instituto Nacional de Cardiologia, Mexico	Patients with CKD 3–4 and uric acid correlates with death but not to ESRD	Madero et al. (2009)
Park et al. (2009)	134, Yonsei University	Uric acid >7 mg/dL correlates with more rapid decline in residual renal function in peritoneal dialysis patients	Park et al. (2009)
See et al. (2009)	28,745, Chang Gung University	Uric acid >7.7 mg/dL in men and >6.6 mg/dL in women only weakly associated with prevalent renal impairment	See et al. (2009)
Noone et al. (2012)	116 children with CKD	Hyperuricemia was associated with 4.6-fold increased risk of progressive CKD as well as elevated BMI and blood pressure	Noone and Marks (2013)
Ejaz (2012)	100 consecutive adult cardiac surgery patients	In comparison to lowest tertile of uric acid, highest had 5-fold risk of AKI during hospital stay	Ejaz et al. (2012)
Ejaz (2012) Li (2014) Rodembach (2015)	26 hyperuricemic cardiac surgery patients randomized to pre-op Rasburicase or placebo 190,718 patients in 14 studies, meta-analysis 627 children enrolled in CKiD Trial	Uric acid reduction results in reduction of post op urinary neutrophil gelatinase associated lipocalin (uNGAL) but no statistically significant difference in plasma creatinine Hyperuricemia conferred an OR 2.35 for new CKD in patients with normal renal function Serum uric acid >5.5 mg/dL independently associated with more rapid decline in GFR	Ejaz et al. (2013) Li et al. (2014) Rodembach et al. (2015)

AKI acute kidney injury, CKD chronic kidney disease, ESRD end-stage renal disease, GFR glomerular filtration rate, NHANES National Health and Nutrition Examination Survey

adult office workers with plasma uric acid in the highest tertile (Nakanishi et al. 2003). In the Osaka Health Study, Tanaguchi et al. demonstrated a twofold increased risk of new

hypertension over 10 years associated with elevated uric acid (Taniguchi et al. 2001). Masuo et al. evaluated the linear association of plasma uric acid and systolic blood pressure, finding an

average increase of 27 mmHg per 1 mg/dl increase in plasma uric acid among nonobese young men (Masuo et al. 2003). In an ethnically diverse population within the **Bogalusa Heart Study**, higher childhood and young adult plasma uric acid levels were associated with incident hypertension and progressive increase in blood pressure even within the normal range (Alper et al. 2005). A post-hoc analysis from the **Framingham Heart Study** also suggested that a higher plasma uric acid level is associated with increased risk of rising blood pressure (Sundstrom et al. 2005). Taken together, the preponderance of evidence supports a close epidemiologic link between uric acid and hypertension that is robust across ethnic racial and anthropomorphic categories but may be attenuated in the elderly.

The epidemiologic link between uric acid and cardiovascular disease is also strong; however, several reports indicate that the link is not statistically independent. However, when multiple regression analysis for confounders including hypertension is performed, the association disappears (Culleton et al. 1999; Moriarity et al. 2000; Sakata et al. 2001; Simon et al. 2006), suggesting the some or all of the impact of uric acid on cardiovascular risk may be mediated through its effects on hypertension.

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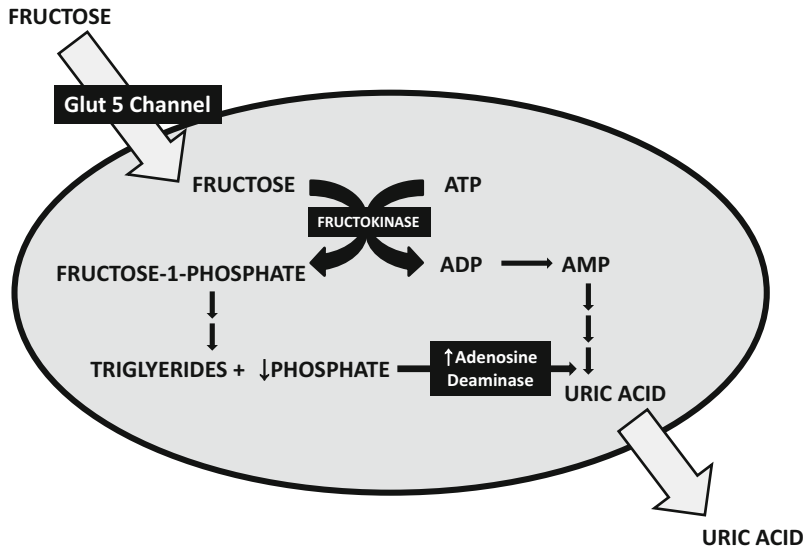
## Uric Acid Metabolism

The causes of hyperuricemia in the young are not well established; however, many possibilities exist – and probably coexist. Increased uric acid can be caused by decreased renal function, resulting in reduced renal urate clearance; in general, children with CKD and ESRD have higher plasma uric acid levels than children with normal renal function (Silverstein et al. 2011). Genetic polymorphisms in anion transporters such as the uric acid anion transporter 1 (URAT-1) (Graessler et al. 2006) and the **SLC2A9** that encodes for GLUT9, an anion transporter with affinity for uric acid (McArdle et al. 2008; Parsa et al. 2012), can lead to hyperuricemia by altering proximal tubular urate clearance. Approximately 15% of uric acid clearance is through the GI tract;

consequently, small bowel disease can also contribute increased plasma uric acid (Cannella and Mikuls 2005). Diets rich in fatty meats, seafood, and alcohol increase plasma uric acid (Lee et al. 2006; Schlesinger 2005), and obesity confers a threefold increased risk of hyperuricemia (Hwang et al. 2006). There are also numerous medications that alter renal clearance of uric acid, even in the presence of normal glomerular filtration rate, including loop and thiazide diuretics (Reyes 2005), and these may represent an uncommon cause of hyperuricemia. Finally, as uric acid is the endpoint of the purine disposal pathway, impairment of the efficiency of purine recycling metabolism or overwhelming the recycling pathway with excessive cell death or cell turnover will increase plasma uric acid (Masseoud et al. 2005).

Serum uric acid levels also correlate with consumption of sweetened food. Sweetener consumption in the USA has dramatically increased since the introduction of **high fructose corn syrup (HFCS)** in the early 1970s (Nakagawa et al. 2006). In hepatocytes, fructose raises the uric acid level rapidly via activation of the **fructokinase** pathway (Fox and Kelley 1972). Fructokinase consumes ATP, leading to an increased load of intracellular purines requiring metabolism and disposal through **xanthine oxidase**–mediated metabolism ending in uric acid (Fox and Kelley 1972; Hallfrisch 1990) (see Fig. 2). The administration of large quantities of fructose to rats, reaching 60% of their caloric intake, results in hyperuricemia, elevated blood pressure, and the development of preglomerular arteriolopathy (Hwang et al. 1987). Furthermore, lowering the uric acid level prevents these changes, despite ongoing fructose consumption (Nakagawa et al. 2006). The requirement for prodigious fructose intake in rats to raise uric acid may be because rats have uricase, an enzyme that metabolizes uric acid to allantoin. Humans are genetically deficient in uricase and thus may require less fructose consumption to result in hyperuricemia.

Human studies show that fructose loading leads to increased plasma uric acid levels acutely and that chronic increases in fructose



**Fig. 2** The effect of cellular fructose metabolism on plasma uric acid. Soluble fructose is taken up into multiple cell types, particularly hepatic cells and adipocytes, via the Glut5 transporter. Fructose is then phosphorylated by fructokinase. Unlike glucokinase, fructokinase does not respond to feedback inhibition by either fructose-1-phosphate or ADP. Consequently, when exposed to sufficiently high concentrations of fructose, intracellular ATP can be

transiently depleted and provide adenosine nucleotide species that are processed by purine disposal pathways that end in uric acid production. The further metabolism of fructose-1-phosphate to glyceraldehyde and dihydroxyacetone phosphate then to triglycerides results in a fall in free phosphate that activates adenosine deaminase, increasing uric acid production. Uric acid exits the cell via one of several anion transporters (Hallfrisch 1990)

consumption lead to chronically elevated serum uric acid and increases in blood pressure (Brown et al. 2008). With the nearly universal exposure to sweetened foods and beverages among children, it is very likely that much of the hyperuricemia that has been observed, especially that associated with **obesity**, is dietary rather than genetic in origin (Nguyen et al. 2009). Consistent with this hypothesis, epidemiological studies have shown a relationship of fructose with serum uric acid in most but not all studies (Jalal et al. 2010). One reason some studies may be negative could reflect the action of fructose, which tends to increase post-prandial uric acid. Some studies measured only fasting uric acid levels, so it is possible that an elevation in mean 24-h uric acid excretion may have been missed.

Jalal and colleagues used the 2000–2003 National Health and Nutrition Examination Survey (NHANES), which was a survey of healthy adults in the USA in which direct blood pressure measurement as well as dietary intake of fructose

as determined by dietary questionnaire were available. They observed a strong, independent relation between fructose intake and elevated systolic blood pressure (Jalal et al. 2010). Interestingly, the finding was independent of fasting serum uric acid levels. In a different study Nguyen and colleagues also found an independent relation between sugary soft drinks and hypertension in adolescents (Nguyen et al. 2009). Perez-Pozo et al. administered 200 g of fructose per day to healthy overweight men with or without allopurinol over a 2 week period (Perez-Pozo et al. 2009). Participants who received only fructose had increases in serum uric acid levels in association with a significant increase in daytime systolic and both 24 h and daytime diastolic blood pressure. Participants who received allopurinol had a decrease in the plasma uric acid levels and the increase in blood pressure was averted. While the dose of fructose was very high in the Perez-Pozo study, 25% of the NHANES cohort actually reported having consumed similar quantities (Jalal et al. 2010).

A recent scientific statement from the American Heart Association strongly recommended reductions in the consumption of dietary sugars during childhood and adolescence as a critical step to prevention of hypertension and cardiovascular disease (Vos et al. 2016).

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### Clinical Trials in Urate Lowering Therapy

A close association has been reported between elevated plasma uric acid and the onset of essential hypertension in adolescents. For example, the Moscow Children's Hypertension Study observed hyperuricemia (>8.0 mg/dl) in 9.5% of children with normal blood pressure, but in 49% of children with borderline hypertension and 73% of children with moderate and severe hypertension (Rovda Iu et al. 1990). The Hungarian Children's Health Study followed all 17,624 children born in Budapest in 1964 over 13 years and reported that elevated heart rate, early sexual maturity, and hyperuricemia constituted statistically significant risk factors for the development of hypertension (Török et al. 1985). These two studies do not separate the hypertensive children by underlying diagnosis, i.e., essential hypertension versus that caused by renal, cardiac, or endocrine causes independent of uric acid, so the relationship between plasma uric and hypertension may be attenuated somewhat. In a small study, Gruskin (Gruskin 1985) compared adolescents (13–18 years of age) with essential hypertension to age-matched, healthy controls with normal blood pressures. The hypertensive children had both elevated plasma uric acid (mean > 6.5 mg/dl) and higher peripheral renin activity. In a racially diverse population referred for the evaluation of hypertension, Feig and Johnson observed that the mean plasma uric acid level ( $\pm$ SD) in controls was  $3.6 \pm 0.8$  mg/dL, similar to that in children with **white coat hypertension** –  $3.6 \pm 0.7$  mg/dl. It was slightly higher in children with secondary hypertension ( $4.3 \pm 1.4$  mg/dl,  $p = 0.008$ ) but significantly elevated in children with primary hypertension ( $6.7 \pm 1.3$  mg/dl,  $p = 0.000004$ ) (Feig and Johnson 2003). There was a tight, linear correlation between the plasma

uric acid levels and the systolic and diastolic blood pressures in the population referred for evaluation of hypertension ( $r = 0.8$  for SBP and  $r = 0.6$  for DBP). Each 1 mg/dl increase in plasma uric acid was associated with an average increase of 14 mmHg in systolic blood pressure and 7 mmHg in diastolic blood pressure (Feig and Johnson 2003). Among patients referred for evaluation of hypertension, a plasma uric acid >5.5 mg/dl had an 89% positive predictive value for essential hypertension, while a plasma uric acid <5.0 had a negative predictive value for essential hypertension of 96% (Feig and Johnson 2003).

Results from small pilot studies in children suggest that uric acid may directly contribute to the onset of hypertension in some people. For example, in one study, five children (Feig et al. 2004), age 14–17 years of age, with newly diagnosed but as yet untreated essential hypertension were treated for 1 month with allopurinol as the solitary pharmacological agent. All five children had a decrease in blood pressure by both casual and ambulatory monitoring, and four of the five were normotensive at the end of 1 month (Feig et al. 2004). In a separate study, 30 adolescents with newly diagnosed essential hypertension were treated in a randomized, double blind crossover trial with allopurinol versus placebo. Sixty-seven percent of children while on allopurinol, and 91% of children with plasma uric acid levels <5.5 mg/dL on treatment, had normal blood pressure, as compared to 3% of children on placebo (Feig et al. 2008).

Such preliminary clinic trial data raise two important questions. First, while allopurinol treatment clearly led to blood pressure reduction, inhibition of xanthine oxidase also reduced superoxide production so that some or all of the effects could plausibly be mediated by reduced oxidant flux. Second, the mechanistic model would suggest that early introduction of uric acid lowering therapy would be optimum, and this was not directly tested. A follow-up clinical trial randomized 60 obese children with prehypertension into three groups to receive placebo, allopurinol, or probenecid, a uricosuric agent (Soletsky and Feig 2012). Children in the placebo group had a slight decrease in casual systolic BP but no significant changes in casual diastolic BP, or ambulatory

blood pressure. In contrast, patients in the active treatment groups experienced marked reduction in SBP average fall of  $-10.1$  and  $-10.2$  mmHg for the allopurinol and probenecid groups, respectively. Similarly, treatment caused a significant fall in casual DBP,  $-8.0$  and  $-8.8$  mmHg, for the allopurinol and probenecid groups, respectively. The same pattern was demonstrated in 24 h ambulatory blood pressure monitoring and adjustment for weight and BMI had no significant effect. These data demonstrate that the mechanism of blood pressure lowering is caused by uric acid reduction and the effects can be demonstrated in children with prehypertension, not just stage 1 hypertension.

Two recent studies, in adults have had contrasting results. Forman and colleagues randomized 72 normotensive adults, mean age 56 years, to allopurinol, probenecid, and placebo. After a 2 month treatment phase, there was no statistically significant difference in ambulatory blood pressure (ASN abstract 2015, submitted to Hypertension) (McMullen et al. 2015). The lack of BP response to urate lowering therapy in an older, lean normotensive population may suggest important vascular differences between adults and younger persons. Alternatively, adults with normal weight and normal blood pressure may have insufficient uric acid-mediated vascular pathology to respond to short-term urate lowering therapy. Gunawardhana and colleagues randomized 102 hypertensive adults with chronic kidney disease to febuxostat, a non-purine xanthine oxidase inhibitor, or placebo. After 6 weeks of therapy, there was no difference in ambulatory blood pressure in the two groups; however, subgroup analysis revealed a significant fall in blood pressure in participants with CKD 1, eGFR  $>90$  ml/min/ $1.73\text{m}^2$ , that was not seen in participants with more advanced renal disease (Gunawardhana et al. 2016). Blood pressure lowering response only in patients with preserved renal function adds further support to the vascular hypothesis.

While these observations require confirmation in larger and more general populations, if plasma uric acid is indeed directly causing renal arteriopathy, altered regulation of natriuresis, and persistent systemic hypertension, it is an important modifiable risk factor for

cardiovascular disease and chronic kidney disease in the absence of other mechanisms.

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## Uric Acid in Chronic Kidney Disease

Historically, the association between uric acid and CKD has been difficult to assess. While hypertension itself and the vasculopathic mechanism proposed to explain uric acid-mediated hypertension (Fig. 1) would be expected to contribute to renal ischemia and glomerular hypoperfusion, decreased glomerular filtration rate itself would increase plasma uric acid, confounding mechanistic conclusions. Several epidemiologic trials have found an association between elevated plasma uric acid and renal functional decline (see Table 4). Bellomo and colleagues followed 900 healthy blood donors, with no history of hypertension or renal disease, for 5 years and found those in the highest quartile of baseline plasma uric acid had an average estimated glomerular filtration rate (eGFR) decline more than  $10$  ml/min/ $1.73\text{m}^2$  greater than those in the lowest plasma uric acid quartile. These findings were sustained through multiple regression and independent of the way eGFR was calculated (Bellomo et al. 2010). An ancillary study to the **Chronic Kidney Disease in Children (CKiD)** Study evaluated the impact of hyperuricemia on children with existing CKD. Higher plasma uric acid,  $>5.5$  mg/dL, was independently associated with increased rate of GFR decline among 627 patients followed in the longitudinal trial (Rodenbach et al. 2015). Among patients with diabetes, elevated uric acid is both a predictor of incident CKD as well as associated with rate of decline in GFR. In a large longitudinal study of 62,830 diabetics, increasing plasma uric acid was associated with increased risk of incident CKD, with as much as a 2.61-fold increased relative risk between lowest and highest quintiles of uric acid (De Cosmo et al. 2015). Among patients with sickle cell disease, elevated uric acid predicts hyperfiltration, progression of CKD, and the development of microalbuminuria (Lebensberger et al. 2016). A recent meta-analysis that surveyed the impact of elevated plasma uric acid in patients

with CKD found that those in the highest quartile of plasma uric acid had both greater progression of CKD and a 1.52-fold increased risk of mortality compared to those with lower plasma uric acid (Xia et al. 2016).

Extreme forms of urate-associated chronic kidney disease are seen in Mesoamerican Nephropathy and Familial Juvenile Hyperuricemic Nephropathy (FJHN). **Mesoamerican Nephropathy** (MN) was initially described in a number of families in Nicaragua and El Salvador. Seen predominantly in sugarcane workers, the chronic exposure to heat stress results in cellular nucleotide release and urate production (Kupferman et al. 2016). This is exacerbated by high fructose exposure in the sugarcane. Soluble uric acid causes glomerular hyperfiltration and hypertrophy and arteriolopathy, and urate crystal precipitation causes renal tubular damage. Repeated exposure to severe acute kidney injury eventually results in chronic kidney disease and end-stage renal disease (Roncal-Jimenez et al. 2016). FJHN is a rare, autosomal dominant disorder involving mutations in the uromodulin gene. This results in a marked reduction in renal urate clearance and severe hyperuricemia. Patients with this genetic disorder develop hypertension and CKD that progresses to ESRD in late adolescence or early adulthood (Alaygut et al. 2013; Vylet' al et al. 2006). Both MN and FJHN cause sufficiently severe hyperuricemia that patients have the characteristics of renal injury from both soluble and crystal urate and can be, in part, managed with allopurinol (Spain et al. 2014).

To date there are few clinical trials that have suggested reduced progression of renal injury in association with uric acid-lowering therapy. Siu and colleagues treated 53 adult men with a pre-treatment mean plasma uric acid of 9.5 mg/dL and observed a trend toward slower functional decline as compared to historical controls ( $\beta = 0.08$ ); however, this study was small and underpowered (Siu et al. 2006). Kanbay and colleagues randomized 59 young adults with CKD to treatment with allopurinol or placebo; those in the active treatment group had a statistically significant increase in GFR in comparison to controls (Kanbay et al. 2007). Uric acid has also been implicated in the

potentiation of acute kidney injury (AKI). Ejaz et al. observed that among adults undergoing cardiac bypass surgery, patients in the highest tertile of plasma uric acid had a fivefold increase in the incidence of AKI (Ejaz et al. 2012a). In a small sample of cardiac bypass surgery patients randomized to preoperative placebo or rasburicase, an enzyme that metabolizes uric acid to allantoin, uric acid reduction was associated with a reduction in levels of the renal injury biomarker NGAL (neutrophil gelatinase associated lipocalin), though no short-term difference in plasma creatinine was seen (Ejaz et al. 2012b).

There are a number of ongoing studies that will address the utility of urate lowering therapy for preservation of renal function. These include the FEATHER and PERL trials. The FEATHER Study is a prospective multicenter, double-blind, randomized trial of the xanthine oxidase inhibitor febuxostat versus placebo in 400 Japanese patients with CKD-3 and plasma uric acid levels 7–10 mg/dL. Patients are being treated with a fixed dose of febuxostat for 2 years. The primary endpoint is slope of GFR decline and the study will be completed in 2018 (Hosoya et al. 2014). **The PERL Study** (Prevention of Early Renal Loss) is prospective multicenter, double-blind, randomized trial in 400 patients with type 1 diabetes mellitus and elevated plasma uric acid. Patients are randomized to the xanthine oxidase inhibitor allopurinol versus placebo for 3 years. The primary endpoint is 30% decline in GFR and the study will be complete in late 2017 (Maahs et al. 2013). It is hoped that the results of these and other studies over the next few years may provide significant insights into the mechanism of uric acid vascular disease as well as its prevention and management.

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## Conclusions

Taken together, a number of epidemiologic studies, animal models, and clinical trials support an association and likely causative role for uric acid in the development of hypertension in some patients with elevated blood pressure. The controversy over the role of uric acid stems from the lack



of a plausible causative mechanism prior to 2001 and its overlap with other more conventional risk factors such as renal disease, diabetes, and obesity. More recent mechanistic studies, however, support uric acid-mediated activation of the renin-angiotensin system, a process with rapid onset that can also be rapidly controlled, followed by a more gradual alteration of renovascular geometry and sodium handling that results in chronic salt sensitive hypertension. The implications of this paired mechanism are twofold. First, it may explain the larger effect seen in younger patients and those with preserved renal function, as compared to older patients and those with advanced CKD. Second, there may be a unique opportunity in patients with newly diagnosed hyperuricemic hypertension, as metabolic control may delay or prevent irreversible vasculopathy and the development of sustained hypertension.

The best way to approach mild to moderate hyperuricemia remains an open question. The currently available medications, especially allopurinol, are associated with significant, even life-threatening, side effects that preclude its safe use in populations as large as those at risk for future hypertension. Furthermore, as there are many classes of readily available antihypertensive medications with more optimal safety profiles so direct management of hypertension is reasonable. The caveat to such an approach is the poor actual control rates in both adult and pediatric hypertension with current conventional approaches bespeaks the need for novel therapeutics. The link between fructose intake and plasma uric acid may also hold important promise; however, while fructose loading clearly leads to increased plasma uric acid and increased blood pressure in clinical trials, the efficacy of fructose reduction in prevention of cardiovascular disease outcomes has not been proven. A post-hoc analysis of the PREMIER trial, a large trial of the efficacy of nonpharmacologic therapy for hypertension and cardiovascular risk mitigation, demonstrated that those participants with the greatest reduction in sweetener consumption also had the greatest reduction in blood pressure (Chen et al. 2010); however, additional research is needed to confirm the results.

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# Insulin Resistance and Other Mechanisms of Obesity Hypertension

# 6

Vidhu V. Thaker and Bonita Falkner

## Abstract

Insulin has important biological effects on the metabolic regulation of carbohydrates, lipids, and proteins. In addition, it has important influences on the vasculature, kidneys, and the sympathetic nervous system. Insulin resistance (or loss of insulin sensitivity) is typically defined as decreased insulin-mediated glucose disposal in the body in response to physiological (endogenous) or exogenous insulin. Insulin resistance is most commonly associated with obesity, although not all obese individuals are insulin resistant, and insulin resistance may be present in nonobese individuals. It can have important adverse consequences on the vasculature and blood pressure, thought to be mediated via vascular inflammation, nitric oxide action, sympathetic nervous system, and renal sodium retention. The “gold standard” for measurement of insulin sensitivity is glucose clamp studies; and the most widely used index for insulin resistance, is the homeostasis model

for insulin resistance (HOMA-IR). The prevalence of insulin resistance and its adverse effects have been found to be higher in children and adolescents with obesity, diabetes, chronic kidney disease, and associated with low-birth weight. Modifications in diet, especially use of DASH diet, physical activity, and drugs such as metformin have been found to be effective in improving insulin resistance. Genetic and epigenetic mechanisms likely influence insulin resistance and are an active area of research.

## Keywords

Insulin resistance • Metabolic syndrome • Obesity • Diabetes • Hypertension • Blood pressure

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## Introduction

Insulin is one of the most potent anabolic hormones that promotes the synthesis and storage of carbohydrates, lipids, and proteins, while simultaneously inhibiting their degradation and release into the circulation (Saltiel and Kahn 2001). The principal role of this peptide hormone is the maintenance of the levels of blood glucose within the normal range of approximately 70–180 mg/dL (4–7 mmol/L) through the cycles of feeding and fasting. This regulation occurs by a complex interplay of metabolic processes that govern nutrient absorption by the intestine, and transport and storage into cells during periods of abundance, while allowing glucose production from protein during periods of fasting in three principal tissues – liver, skeletal muscle, and adipose tissue. In addition to the regulation of glucose, insulin exerts important biologic actions in the vasculature and within the kidney (Lastra-Lastra et al. 2009). Insulin resistance (or the inverse of insulin sensitivity) is typically defined as decreased insulin-mediated glucose disposal in the body in response to physiological (endogenous) or exogenous insulin (Levy-Marchal et al. 2010). Within the target organs, there is decreased glucose uptake and glycogenesis in myocytes, increased lipolysis via decreased antilipolytic activity in adipocytes, and decreased inhibition of glycogenolysis and increased gluconeogenesis in hepatocytes (Groop et al. 1989; Kelley and Simoneau 1994).

Insulin resistance is most commonly associated with obesity, although not all obese persons are insulin resistant, and insulin resistance may be present in nonobese people. It may also be seen in certain physiological states such as pregnancy and puberty. Due to the impaired insulin-

mediated glucose uptake, greater amounts of insulin are secreted to achieve glucose regulation. The resulting chronic hyperinsulinemia imposes dysregulatory effects on the other target tissues and organs such as kidney and the microvasculature. Hyperinsulinemia is associated with enhanced renal sodium reabsorption. In the context of the vascular system, insulin resistance manifests as endothelial dysfunction, impaired vascular smooth muscle action, and vascular inflammation. (Nigro et al. 2006; Schulman and Zhou 2009). Thus, impairment of the vascular insulin-signaling pathway (vascular insulin resistance) may be a triggering factor in the initiation of cardiovascular disease in insulin resistance syndromes such as obesity and type 2 diabetes.

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## Postulated Mechanisms for Insulin Resistance Leading to Hypertension

The effects of insulin on the vasculature can result in either vasoprotection or vascular injury, depending on the pathophysiological state and the involved cell types. These diametrically opposite effects appear to be caused by the dose-dependent action of insulin on two different pathways. At the relatively lower fasting levels seen in insulin-sensitive persons (typically 50–150 pM), insulin constitutively stimulates the phosphatidylinositol-3-kinase (PI3K) signaling pathway that participates in regulating its metabolic effects and maintaining the vascular tone. In insulin-resistant states, in which the fasting insulin levels may reach nano- to micromolar range, the PI3K pathway is selectively impaired, activating the alternative mitogen-activated protein kinase (MAPK) signaling pathway, increasing vasoreactivity (and leading to hypertension) and vascular growth (with resultant stiffening or hypertrophy), both of which are implicated in the development of long-term macro- and microvascular complications (Nigro et al. 2006; Schulman and Zhou 2009).

The binding of insulin to the insulin receptor substrate (IRS, specifically IRS-1) results in tyrosine phosphorylation activating PI3K that causes NO production via the endothelial nitric oxide synthase (eNOS) activity. NO, in turn, is thought to mediate the vasoprotective effects of insulin including vasodilation, inhibition of vascular smooth muscle cell (VSMC) migration and proliferation, attenuation of inflammatory cell infiltration into the vascular wall, and inhibition of platelet aggregation (Kim et al. 2006; Muniyappa et al. 2007). This hypothesis is supported by the observation of vasodilation in *in vitro* aortic preparations that is impaired in type 2 diabetic mice (Baron et al. 1996). In VSMCs, insulin regulates NO production by the inducible NO synthase (iNOS) that maintains vascular tone (Nigro et al. 2006). Additionally, it inhibits vascular contractility by attenuating increases in cytosolic calcium channels and stimulating the activity of myosin light-chain phosphatase (Schulman and Zhou 2009). It is also possible that these effects are augmented by NO-mediated glucose disposal, as glycemic control itself serves as protection against inflammation (Dandona et al. 2007).

The activation of MAPK pathway in the insulin-resistant state results in the stimulation of secretion of the vasoconstrictor endothelin (ET-1) in the vascular endothelium (Eringa et al. 2004; Scherrer and Sartori 1997), and endothelial expression of cellular adhesion molecules (e.g., plasminogen activator inhibitor-1 (PAI-1), vascular cell adhesion molecule (VCMA-1), monocyte chemoattractant protein (MCP-1), and E-selectin). Together, these molecules exert detrimental effects on the vascular wall by inducing endothelial dysfunction and fostering atherosclerosis. In cultured VSMCs, insulin stimulates the expression of angiotensinogen via the MAPK pathway, activating the renin-angiotensin pathway, especially with production of Ang-II and activation of its receptor, AT<sub>1</sub>R (Kamide et al. 2004; Tuck et al. 2004). Insulin resistance impairs stimulation of the PI3K pathway, and synergistically stimulates the MAPK pathway promoting

cardiovascular disease (Nigro et al. 2006). Hyperinsulinemia also causes vasoconstriction by activation of the sympathetic nervous system and stimulation of secretion of the vasoconstrictor ET-1 in the vascular endothelium (Eringa et al. 2004; Scherrer and Sartori 1997).

In the kidney, insulin has been shown to act on various segments of the nephron, with the predominant action of renal sodium reabsorption. In normal individuals, this may not cause hypertension possibly due to the simultaneous NO-mediated vasodilation. In states of chronic hyperinsulinemia, the vasodilator action is lost with continued sodium reabsorption mediated by sodium transport channels as well as by the activation of the renin-angiotensin-aldosterone pathway, tumor necrosis factor- $\alpha$ , and with-no-lysine kinases (WNK) (Horita et al. 2011). Evidence from clinical studies on the effects of insulin resistance is discussed in subsequent sections.

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## Measurement of Insulin Resistance

Due to the importance of insulin resistance in physiology and disease, a wide range of measurement methods have been devised. All methods that assess insulin-mediated glucose disposal can be quantified using combination(s) of insulin and glucose levels in the blood along with other physiological parameters. Most of the currently available methods measure peripheral insulin resistance, mainly in the skeletal muscle, although some methods may give an estimate of the hepatic insulin resistance.

Since the assessment of insulin resistance depends on the measured insulin levels, it is worthwhile emphasizing the importance of an accurate assay, especially in the lower ranges seen in the fasting state. Besides the importance of using non hemolyzed samples, it is noteworthy that the insulin levels are higher in the serum compared to plasma samples, (Manley et al. 2007). Hence, uniformity of sample ascertainment



within a study is important. Additionally, it is beneficial to follow the guidelines of the Insulin Standardization Work Group to report the results in International Units (SI, pmol/L), to maintain the precision, accuracy, and replicability across studies (Staten et al. 2010). Fasting insulin levels can provide evidence of compensatory hyperinsulinemia, but are not a good measure of peripheral insulin sensitivity. Such levels show wide variability in different persons, not always correlated with the currently accepted reference standards for insulin sensitivity (George et al. 2011), and, in isolation, are not a good measure of insulin resistance (Levy-Marchal et al. 2010). Clinical features such as acanthosis nigricans can indicate a likelihood of insulin resistance, but cannot define it.

The “gold standard” method for measurement of insulin resistance in adults is the glucose clamp technique (DeFronzo et al. 1979), which has been adapted for children and adolescents. In the hyperinsulinemic euglycemic clamp, insulin (I) is infused in one arm to maintain hyperinsulinemia at a level that suppresses hepatic glucose production (generally an insulin level above 40–60 mU/m<sup>2</sup>/min in nondiabetic patients with normal BMI, and ≥ 80 mU/m<sup>2</sup>/min in obese persons). The insulin infusion is accompanied by an infusion of 20% dextrose titrated to maintain euglycemia (blood glucose (BG) ~80–100 mg/dL). Euglycemia is accomplished through frequent BG measurements in “arterialized blood” from the warmed contralateral extremity. At steady state, the glucose infusion rate is equal to the insulin-mediated glucose uptake rate (M) in mg/kg/min. M is then adjusted for the actual plasma level of steady-state achieved insulin (I). Insulin sensitivity is then expressed as M/I. Higher M/I indicates greater insulin sensitivity, and lower M/I is consistent with insulin resistance. Since most of the glucose uptake occurs in skeletal muscles, the glucose clamp method may underestimate insulin sensitivity in obese persons. M/I can be adjusted for fat-free or lean body mass to achieve a more accurate estimation of insulin-

mediated glucose uptake. However, Gniuli et al. have shown that adipose tissue may contribute significantly to insulin-mediated glucose uptake in morbidly obese subjects (Gniuli et al. 2010).

The frequently sampled IV glucose tolerance test (FSIVGTT) (Bergman et al. 1987; Pacini and Bergman 1986) and steady-state plasma glucose (SSPG) (Shen et al. 1970) are other valid measurements in adults that have been studied in limited cohorts of children. These methods are invasive, and several simpler methods, based on the oral glucose tolerance test (OGTT), or fasting plasma glucose and insulin levels have been developed for larger epidemiological studies (Table 1). The homeostasis model for assessment of insulin resistance (HOMA-IR) is an estimate of insulin resistance derived from fasting glucose and insulin levels. It has been validated as a surrogate measure of insulin resistance with a correlation as high as 0.91 with glucose clamp studies and FSIVGTT (Conwell et al. 2004; Gungor et al. 2004; Keskin et al. 2005).

HOMA-IR =

$$\frac{\text{Fasting insulin}(\text{microU/L}) \times \text{Fasting glucose}(\text{nmol/L})}{22.5}$$

The calculated HOMA-IR value is an estimate of insulin resistance, unlike the calculated M/I value based on an insulin clamp procedure which measures insulin sensitivity. Therefore higher HOMA values indicate greater insulin resistance, although there is no specific threshold HOMA-IR value that is diagnostic of insulin resistance.

Population-based norms are available for children and adolescents older than 12 years of age (Lee et al. 2006), derived from the analysis of data from 1,802 adolescents from the NHANES 1999–2002. In the NHANES data, the prevalence of insulin resistance was much higher in obese children (BMI ≥ 95th percentile, mean 4.93 [95% CI 4.56–5.35]) compared with those of normal weight (BMI < 85th percentile, mean 2.30 [95% CI 2.21–2.39]). Weight status was the most important determinant of insulin resistance,

**Table 1** Summary of the current methods for measuring insulin resistance

Indices (Reference)	Formulas	Units
<b>Based on clamp</b>		
<b>Metabolized glucose (M)</b> (DeFronzo et al. 1979)	$M = INF - SC$ , where <i>INF</i> is the glucose infusion rate and <i>SC</i> is the space correction, accounting for the variation in glucose concentration; $SC = (G_2 - G_1) \times 0.095$ , where $G_2$ and $G_1$ are the glucose concentrations at the end and the beginning of the interval	Glucose infusion rate = mg/kg.min; Glucose = mg/dL
<b>IS</b> (DeFronzo et al. 1979)	$IS = GIR_{ss}/G_{ss} \times \Delta I_{ss}$ , where <i>GIR</i> is the steady-state glucose infusion rate, <i>G<sub>ss</sub></i> is the steady-state blood glucose concentration, and the $\Delta I_{ss}$ is the difference between steady-state and basal insulin concentrations	Glucose infusion rate = mg/kg.min; Glucose = mg/dL; Insulin = $\mu$ U/mL
<b>Based on OGTT</b>		
<b>ISI Gutt</b> (Gutt et al. 2000) <sup>a</sup>	$\{75,000 + (\text{fasting glucose} - 2\text{-h glucose}) \times 0.19 \times BW\} / \{120 \times \log([\text{fasting insulin} + 2\text{-h insulin}]/2) \times (\text{fasting glucose} + 2\text{-h glucose})/2\}$ , where <i>BW</i> is body weight	Glucose = mg/L; BW = kg; Insulin = $\mu$ U/mL
<b>ISI Matsuda</b> (Matsuda and DeFronzo 1999) <sup>b</sup>	$10,000 / [\text{square root}(\text{fasting glucose} \times \text{fasting insulin}) \times (\text{mean glucose} \times \text{mean insulin})]$	Glucose = mg/dL; Insulin = $\mu$ U/mL
<b>ISI Cederholm</b> (Cederholm and Wibell 1990) <sup>a</sup>	$[75,000 + (\text{fasting glucose} - 2\text{-h glucose}) \times 1.15 \times 180 \times 0.19 \times BW] / [120 \times \log(\text{mean insulin}) \times \text{mean glucose}]$ , where <i>BW</i> is body weight	Glucose = mmol/L; BW = kg; Insulin = $\mu$ U/mL
<b>ISI Stumvoll</b> (Stumvoll et al. 2000) <sup>a</sup>	$0.226 - 0.0032 \times \text{BMI} - 0.0000645 \times 2\text{-h insulin} - 0.00375 \times 1.5\text{-h glucose}$	Glucose = mmol/L; BMI = kg/m <sup>2</sup> ; Insulin = pmol/L
<b>OGIS</b> (Mari et al. 2001) <sup>b</sup>	Calculated from OGTT using the formula available at <a href="http://www.ladseb.pd.cnr.it/bioing/ogis/home.html">www.ladseb.pd.cnr.it/bioing/ogis/home.html</a>	Conventional or SI units
<b>ISI Belfiore</b> (Belfiore et al. 1998) <sup>a</sup>	$2 / \{[(\text{AUC insulin}) \times (\text{AUC glucose})] + 1\}$ , where <i>AUC insulin</i> and <i>AUC glucose</i> represent the area under the insulin curve and area under the glucose curve divided by mean of normal values	Conventional or SI units
<b>ISI Avignon</b> (Avignon et al. 1999) <sup>a</sup>	$\{[0.137 \times 100,000,000 / (\text{insulin}_{T_0} \times \text{glucose}_{T_0} \times \text{VD})] + [100,000,000 / (\text{insulin}_{T_{2h}} \times \text{glucose}_{T_{2h}} \times \text{VD})]\} / 2$ , where <i>VD</i> is the apparent glucose distribution volume = 150 (mL/kg) $\times$ BW (kg)	Glucose = mg/dL; Insulin = $\mu$ U/mL
<b>SI<sub>is</sub>OGTT</b> (Bastard et al. 2007) <sup>a</sup>	$1 / [\log(\text{sum glucose}_{t_{0-30-90-120}}) + \log(\text{sum insulin}_{t_{0-30-90-120}})]$	Glucose = mmol/L; Insulin = $\mu$ U/mL
<b>Log sum insulin</b> (Cheng et al. 2004) <sup>b</sup>	$\log(\text{sum insulin}_{t_{0-30-60-120}})$	Insulin = $\mu$ U/mL
<b>Based on fasting samples</b>		
<b>HOMA</b> (Matthews et al. 1985)	$(\text{Fasting insulin} \times \text{fasting glucose}) / 22.5$	Glucose = mmol/L; Insulin = $\mu$ U/mL
<b>QUICKI</b> (Katz et al. 2000)	$1 / (\log \text{fasting insulin}) + (\log \text{fasting glucose})$	Glucose = mg/dL ; Insulin = $\mu$ U/mL
<b>Fasting insulin</b>		Insulin = $\mu$ U/mL

Adapted from Henderson et al. Diabetes and Metabolism 2011

<sup>a</sup>Based on 2-h OGTT; <sup>b</sup>Based on both 2-h and 3-h OGT

accounting for 29.1% of the variance in HOMA-IR. Girls and Mexican-American adolescents were found to have higher levels of HOMA-IR, while no differences were found

between black and white children. These standards from NHANES can serve as a guide, but are not currently recommended for use in individual patients clinically.

## Insulin Resistance in Obesity-Associated Hypertension

The prevalence of hypertension in children and adolescents has increased in parallel with the childhood obesity epidemic (Din-Dzietham et al. 2007; Muntner et al. 2004). While the current estimates of childhood hypertension based on repeated blood pressure (BP) measurements approximate 3.5%, the prevalence is higher among overweight and obese children and adolescents (BMI  $\geq$  95th percentile). Data from a study on high school students reveal combined prevalence rates of hypertension and prehypertension, now termed elevated BP, higher than 30% in obese adolescent boys and between 23–30% in obese adolescent girls, depending on the ethnicity (McNiece et al. 2007). Several other reports confirm the higher prevalence of high BP among obese children compared to normal weight children (Falkner et al. 2006; Schwandt et al. 2015; Sorof and Daniels 2002). There is a consistent positive relationship between body size and BP level throughout childhood. Tu et al. showed that in a cohort of healthy children, the prevalence of elevated BP (>90th%) increased by fourfold beyond the 85th percentile of BMI (Tu et al. 2011). Thus, in addition to the obese, overweight children are also at an increased risk of high BP.

## Metabolic Syndrome

Close to 30 years ago, the concomitant presence of obesity, hypertension, type 2 diabetes, and atherosclerosis began to be recognized in individual adult patients. Originally described as Syndrome X by Reaven in 1988 (1988), this cluster of conditions is now designated as Metabolic Syndrome (MetS). Insulin resistance, or impaired insulin-mediated glucose uptake, is now established as the core abnormality that links the metabolic and hemodynamic abnormalities in this condition (DeFronzo and Ferrannini 1991). Because insulin resistance has been difficult to quantify clinically, the concept of metabolic syndrome developed as a strategy to identify persons with multiple

cardiovascular risk factors that are linked with insulin resistance (Meigs et al. 1997; Yip et al. 1998). Several reports have demonstrated a heightened risk for diabetes and cardiovascular disease among adults with metabolic syndrome (Lakka et al. 2002; Meigs et al. 2006).

There has been some variation in the precise definition of MetS regarding both included risk factors and the values considered to be abnormal. Among various definitions, the World Health Organization (WHO) (Alberti and Zimmet 1998) and the National Cholesterol Education Program Adult Treatment Panel III (ATPIII) (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001) criteria are more commonly used in clinical reports in adults. According to the ATPIII definition, metabolic syndrome is present if an adult meets three of the five following criteria: (1) visceral obesity based on waist circumference, (2) elevated BP, (3) abnormal glucose tolerance, (4) elevated plasma triglyceride, (5) low high-density lipoprotein (HDL-cholesterol).

Although it has been recognized that abnormal levels in BP, adiposity, and lipids can be detected in childhood, no consistent definition of MetS has been established for children and adolescents. Reports on the prevalence of MetS in children have generally been based on modifications of ATPIII or WHO definitions (Bergström et al. 1996; Goran et al. 2003; Weiss et al. 2004; Young-Hyman et al. 2001). Obesity is commonly associated with insulin resistance in childhood manifested by relative hyperinsulinemia (Caprio 2002). Cook et al. investigated the prevalence of MetS in children and adolescents based on the data from the NHANES data periods 1988–1994 (Cook et al. 2003). Based on the ATPIII criteria modified for children, the investigators reported an overall prevalence of MetS at 4.2% in children and adolescents. However, among obese adolescents the prevalence was as high as 28.7%. It is of note that the data periods 1988–1994 preceded the childhood obesity epidemic and as expected, higher rates of MetS are associated with the increasing prevalence of childhood obesity. In a study on a predominantly obese cohort of children

and adolescents, Weiss et al. reported that the prevalence of MetS increased with severity of obesity and reached 50% among severely obese youth (Weiss et al. 2004). Another study on a cohort of obese children found elevated BP ( $\geq 90$ th percentile), by repeated BP measurement, in 37% of the cohort. More boys with high BP had low HDL-cholesterol compared to boys with normal BP (49.4 versus 27.6%). The rates of high BP and low HDL-cholesterol both increased among the more severely obese boys and girls (Boyd et al. 2005). Other reports also describe the cluster of high BP, dyslipidemia, and hyperinsulinemia commonly detected in obese children and adolescents (Sinaiko et al. 2002, 1997). Thus, childhood obesity, with underlying insulin resistance, commonly manifests multiple cardiovascular and metabolic risk factors that are related to atherosclerosis. Pathologic evidence of early atherosclerotic lesions in the aorta and coronary arteries were identified in autopsy studies in the youth following premature death associated with multiple risk factors consistent with MetS (Berenson et al. 1998). These reports indicate that the constellation of metabolic risk factors detectable in obesity-associated hypertension accelerate the risk for cardiovascular disease in early adulthood.

### **Mechanism for Obesity-Associated Hypertension**

Multiple theories have attempted to explain the link between obesity and hypertension. It has been proposed that hyperinsulinemia, a consequence of insulin resistance, activates sympathetic nervous system (SNS) activity (Esler et al. 2006). Based on experimental models, a potential mechanism for SNS activation could be adipose tissue production of leptin, which is commonly elevated in obese individuals (DiBona 2013). Further support of heightened SNS activity in obese hypertensive children has been developed with the application of 24-h ambulatory blood pressure monitoring (ABPM). Compared to normal weight hypertensive children, obese hypertensive children have

higher heart rates and greater BP variability during ABPM, indicative of a hyperkinetic hemodynamic condition (Sorof and Daniels 2002). In recent reports, investigators applied advanced Fourier analysis to 24-h ABPM data and detected variations in the cardiac rhythms in hypertensive children (Litwin et al. 2010a,b). In a longitudinal study on obese hypertensive youth by Niemirska et al., abnormal BP rhythmicity detected before treatment was unchanged with pharmacologic therapy that reduced BP, but the abnormal BP rhythmicity was normalized among patients who lost weight (Niemirska et al. 2013). Overall, the evidence indicates that there is, at least in part, a role of SNS activity in the link between obesity and hypertension in childhood, as well as adulthood. These observations also support the benefit of weight reduction in children and adolescents with obesity-associated hypertension.

Dietary sodium has been implicated in obesity-associated hypertension in childhood. In a recent analysis of childhood BP trends from sequential NHANES data periods 1988–2008, Rosner et al. demonstrated a progressive increase in both the BP level and the prevalence of high BP in children and adolescents (Rosner et al. 2013). In this analysis, the predictors of this increase were BMI, waist circumference, and dietary sodium intake. Thus, it appears that sodium intake, in addition to obesity, is contributing to higher levels of BP in children. This observation is further supported by a report by Yang et al. on dietary sodium intake data from NHANES 2003–2008 (Yang et al. 2012). In a sample of over 6,000 children and adolescents, of whom 37% were overweight or obese (BMI  $\geq 85$ th percentile), the average sodium intake was 3,387 mg/day. The study group was stratified according to quartile of dietary sodium intake and within each quartile separated by normal weight and overweight/obese. For the entire population each 1,000 mg/day of sodium intake was associated with about 1.0 mmHg increase in systolic BP; whereas, among the overweight/obese subjects, systolic BP increased 1.5 mmHg for each 1,000 mg/day sodium intake. For the entire cohort the adjusted odds ratios

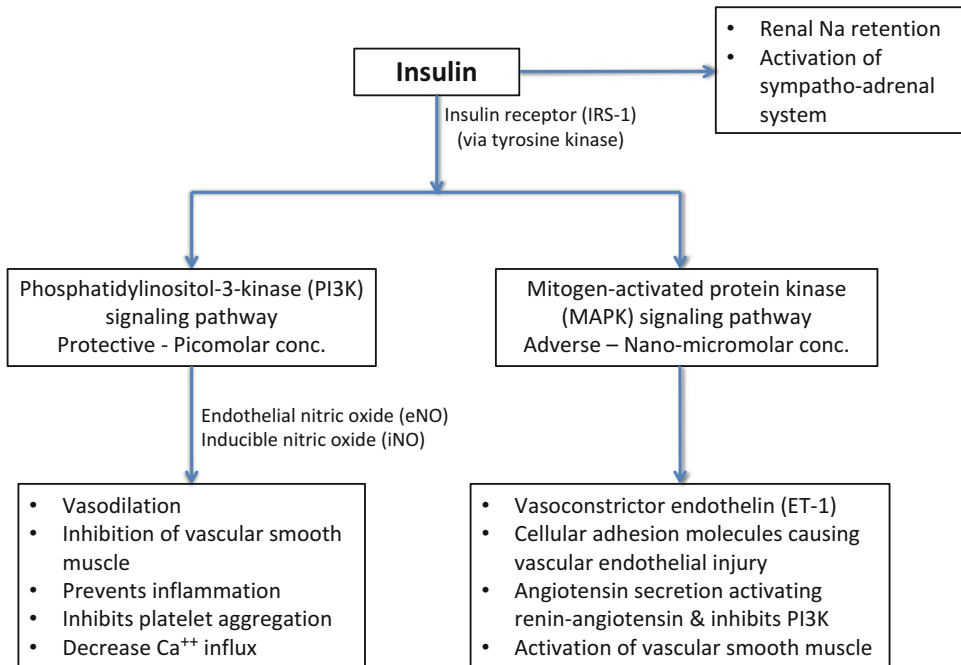
(OR) comparing risk for prehypertension/hypertension in the highest sodium intake quartile compared to the lowest was 2.0 (95% CI = 0.95–4.1;  $P = 0.062$ ). However, among the overweight/obese children, the adjusted OR for prehypertension/hypertension in the high sodium intake quartile increased to 3.5 (95% CI = 1.3–9.2;  $P = 0.013$ ). As proposed by the investigators, in children, overweight/obesity and sodium intake appeared to have synergistic effects on risk for high BP.

Experimental and clinical studies demonstrate that insulin upregulates sodium transport in distal renal tubules (Tiwari et al. 2007). As described earlier, obese children, as well as adults, tend to have relative hyperinsulinemia secondary to obesity-associated insulin resistance. Higher insulin levels enhance sodium reabsorption, a process that can result in higher BP. This concept was supported by Rocchini et al. on a sample of obese children with elevated BP (Rocchini et al. 1989). The obese children had BP measurements following 2 weeks on a high salt diet and again following a low salt diet. There was a significant decrease in BP on the low salt diet, indicating BP sensitivity to sodium intake. Subsequently the children underwent a weight reduction intervention for several weeks after which the high and low salt diet procedures were repeated. For participants who experienced a modest weight reduction, there was decrease in the BP reduction following the change from the high salt to low salt diet indicating a reduction in BP sensitivity to sodium. Among those with no weight change the BP response was the same. These findings support the concept of a renal mechanism with BP sensitivity to sodium likely mediated by insulin. The results also provide evidence that weight loss appears to blunt sodium sensitivity in obese children, and that weight loss is a reasonable therapeutic goal in obese children. The literature on dietary salt intake and BP in children is limited compared to that in adults. But, the emerging evidence supports a causative role of high sodium intake on elevated BP, especially in the presence of overweight and obesity.

A clue to a possible genetic mechanism for renal regulation of sodium sensitivity in obese

children was reported in a study conducted on cohort of children in China (Xi et al. 2013). In this study the investigators constructed a genetic risk score (GRS) based on six single nucleotide polymorphisms (SNPs) from prior GWAS studies on hypertension. They found an association of three SNPs and the GRS with higher systolic BP and four SNPs with hypertension in the obese group, that was not seen in the normal weight children. Of interest, three of the four SNPs found to be significantly associated with BP in obese children have been reported to be linked with renal sodium regulation (Xi et al. 2013).

Another possible mechanism for obesity-associated hypertension is alteration in microvascular function and structure. Elevations in plasma levels of pro-inflammatory cytokines, such as C-reactive protein (CRP) and interleukin-6 (IL-6), are associated with obesity (Lyon et al. 2003). Similar elevations of inflammatory cytokines are reported in obese children (DeLoach et al. 2014; Weiss et al. 2004). In humans, obesity is associated with accumulation of macrophages in adipose tissue, which may contribute to obesity-related inflammation (Wu et al. 2007). Support for a causal role of inflammation in development of hypertension is based largely on experimental studies that focus on endothelial dysfunction (Guzik et al. 2007; Madhur et al. 2010; Vaughan et al. 1995). Exposure of human vascular endothelial cells to CRP in vitro results in decreased expression of endothelial nitric oxide synthase with attenuation of vasodilation in response to provocative stimuli (Venugopal et al. 2002). Recent experimental studies describe a role of perivascular adipose tissue (PVAT) in paracrine signaling of inflammatory cytokines. Excess PVAT contributes to endothelial dysfunction and increased vascular smooth muscle tone (Houben et al. 2012; Marchesi et al. 2009). In vitro experiments on PVAT from obese and lean humans demonstrate that vasodilatory capacity is lost in PVAT from obese subjects with concurrent expression of mediators of inflammation and oxidative stress (Greenstein et al. 2009). Thus, microvascular dysfunction, mediated by PVAT-derived inflammation, could contribute to the insulin resistance and capillary rarefaction, both of



**Fig. 1** Simplified depiction of mechanism(s) of insulin resistance

which set the stage for increased vascular resistance and hypertension.

The elaborated mechanisms underlying obesity-associated hypertension likely overlap or act synergistically (Fig. 1). Despite many gaps in the complete understanding of these mechanisms, it is clear that obesity-induced insulin resistance in childhood has many adverse effects that lead to premature adult onset cardiovascular and metabolic disease.

### Insulin Resistance in Chronic Kidney Disease (CKD)

An association of insulin resistance with CKD has been demonstrated both experimentally and clinically (DeFronzo et al. 1981). The metabolic consequences of insulin resistance/hyperinsulinemia are considered to be related to the elevated risk for accelerated atherosclerosis in adults with CKD. Reports from population studies describe an association of MetS with CKD in adults with an increasing prevalence of MetS as kidney function declines (Beddhu et al. 2005; Chen et al. 2004).

Several causal factors for insulin resistance have been considered, including uremic toxins, elevated uric acid, and inflammation. Recent studies have developed novel insights on mechanistic pathways in development of insulin resistance in CKD.

Adipose tissue serves the endocrine function in production of several cytokines and hormones designated as adipokines. Adipocytes produce several inflammatory cytokines including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ), and plasminogen activator inhibitor type-1 (PAI-1), along with adiponectin, a hormone that has anti-inflammatory, anti-atherosclerotic, and insulin-sensitizing properties. There is a consistent strong relationship of elevated circulating pro-inflammatory cytokines with obesity. However, plasma levels of adiponectin are significantly lower among obese individuals with normal kidney function compared to normal weight individuals with normal kidney function (Weyer et al. 2001). While obesity-associated inflammation had been thought to contribute a causal role in the insulin resistance of obesity, recent studies in adults and in children (Weiss et al. 2004)

demonstrate that pro-inflammatory cytokines are significantly associated with obesity, but pro-inflammatory cytokines do not have an independent association with insulin resistance. These clinical studies, using the insulin clamp procedure (Martinez Cantarin et al. 2011) or oral glucose tolerance test (Weiss et al. 2004), demonstrate a significant independent association of adiponectin with insulin resistance, findings consistent with the insulin-sensitizing activity of adiponectin.

Despite, evidence of insulin resistance in CKD, plasma levels of adiponectin are elevated in patients with CKD, a relation that is independent of obesity or BMI (Nanayakkara et al. 2009). Several suggested explanations for the opposite relationship of adiponectin with insulin resistance in CKD considered reduced renal clearance of adiponectin, chronic malnutrition, or a response to uremic inflammation (Cui et al. 2011). While adiponectin is secreted by adipose tissue, adiponectin receptors (adipoR1 and adipoR2) are predominantly expressed in muscle and liver where they exert their major antidiabetic functions. A study by Martinez Cantarin et al. reported increased adiponectin secretion in patients with end-stage renal disease (ESRD) that was associated with elevated plasma levels of adiponectin (Martinez Cantarin et al. 2013). These investigators conducted studies on human tissues harvested from ESRD patients and healthy kidney donors at the time of renal transplantation. Their data demonstrate an increase in adiponectin protein and mRNA expression level in subcutaneous and visceral adipose tissue, as well as increased mRNA expression of the adiponectin receptors in fat and muscle in ESRD patients compared to controls with normal kidney function. Data in subsequent *in vivo* and *in vitro* studies by these investigators demonstrated disruption in the normal adiponectin signaling pathway in muscle cells in uremia, consistent with adiponectin resistance at the post-receptor level (Martinez Cantarin et al. 2014). These reports support the concept that the insulin resistance observed in CKD is a consequence of loss of an adiponectin insulin-sensitizing function due to adiponectin resistance. Further studies will be needed to delineate the

mechanistic pathway of adiponectin resistance in CKD.

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## Diabetes, Insulin Resistance, and Hypertension

The vast majority of patients with type 2 diabetes (T2D) have insulin resistance. Fasting hyperglycemia, the hallmark of T2D, develops with the failure of the pancreatic  $\beta$ -cell to sustain compensatory hyperinsulinemia to maintain glucose homeostasis in the face of insulin resistance (Reaven 2011). Based on the mechanistic links between insulin resistance and hypertension considered above, it is no surprise that many patients with T2D also have hypertension. Additionally, multiple studies have provided evidence that insulin resistance is also involved in the development of adverse long-term micro- and macrovascular complications in patients with type 1 diabetes (T1D), classically considered a disease of insulin deficiency (DeFronzo et al. 1982a; Donga et al. 2013; Nadeau et al. 2010; Specht et al. 2013).

Cross-sectional studies in youth have shown a high prevalence of hypertension in both those with T1D and T2D. In the population-based multicenter SEARCH study of youth aged 3–17 years, 5.9% of participants with T1D and 23.7% of those with T2D had elevated blood pressure (Rodriguez et al. 2010). In the TODAY study, the largest longitudinal systematic multicenter study of youth with T2D, 699 adolescents between 10–17 years of age were enrolled within 2 years of the diagnosis of T2D. Participants in the TODAY cohort were randomized to receive metformin only, metformin plus lifestyle intervention, or metformin plus rosiglitazone therapy (Study Group 2013). At baseline, 11.6% of the participants were hypertensive, and over a mean follow-up period of 3.9 years, the prevalence increased to 33.8% (Study Group 2013). Older age, male sex, and higher BMI at baseline were associated with a higher risk of developing hypertension. The development of hypertension was not influenced by the treatment type, race/ethnicity, or the occurrence of glycemic failure.

Previous discussion on the mechanism of insulin resistance and hypertension are also relevant to diabetes. It is postulated that there are differences in insulin sensitivity in various target tissues. In patients with T2D there is resistance to insulin-mediated glucose uptake in liver and muscle tissue resulting in hyperinsulinemia. The relative hyperinsulinemia necessary for glucose regulation can disrupt the normal physiology of other tissues that are not resistant to insulin. The renal response to hyperinsulinemia is upregulation of sodium retention (Facchini et al. 1999). Hyperinsulinemia also impacts the sympathetic nervous system, resulting in both vasoconstriction and sodium retention (Reaven 1997; Reaven et al. 1996).

In patients with type 1 diabetes, the lack of endogenous insulin makes it difficult to assess insulin resistance, especially since the simpler tools such as the homeostasis model are not applicable. The association of decreased insulin sensitivity with vascular disease and hypertension was first reported in late 1960s. Martin and Warne described poorer prognosis in patients with clinically evident vascular disease and hypertension, when associated with lower glucose assimilation index, as measured by fall in blood glucose after a standardized dose of intravenous insulin (Martin and Warne 1975). DeFronzo et al. demonstrated the presence of hepatic and peripheral insulin resistance in adults with T1D, using euglycemic-hyperinsulinemic clamp studies (DeFronzo et al. 1982a; DeFronzo et al. 1982b).

Newer methods to estimate insulin sensitivity in T1D such as estimated Glucose Disposal Ratio (eGDR) (Williams et al. 2000) and the Insulin sensitivity score (IS) (Dabelea et al. 2011), with easily measurable parameters like hypertension, waist-hip ratio, lipid levels, and family history of hypertension, were devised based on their correlation with glucose disposal in clamp studies and subsequently validated in independent cohorts. The 10-year historical prospective data obtained from the Pittsburgh Epidemiology of Diabetes Complications Study of 603 patients with T1D (onset below 18 years of age) found that cardiovascular events were related to insulin resistance-

related factors rather than to glycemic control per se (Orchard et al. 2003). Analysis of the data collected during the Diabetes Control and Complications Trial (DCCT), a 9-year follow-up study of 1,441 participants with T1D designed to compare intensive insulin treatment versus conventional blood glucose management, showed increased risk of both micro- and macrovascular complications in those participants with greater insulin resistance at baseline as estimated by lower eGDR. The term “double diabetes” has been coined to describe the patients with T1D who also have evidence of insulin resistance, elicited by testing with eGDR (Kilpatrick et al. 2007). In another publication from the DCCT, the prevalence of hypertension and MetS increased most in those patients in the intensive insulin therapy arm who gained the most weight over time (Purnell et al. 1998). Adjusting for the prevalence of MetS and the insulin dose, the risk of developing the complications of diabetes was higher over time in patients with lower baseline eGDRs, showing the relation between insulin resistance and microvascular disease (Kilpatrick et al. 2007). This association has also been consistently demonstrated in youth with T1D. Nadeau et al. noted higher prevalence of insulin resistance measured by hyperinsulinemic clamp, impaired functional exercise capacity, and cardiovascular dysfunction in a cohort of 12 adolescents with T1D when compared with controls (Nadeau et al. 2010). In another study of 291 patients with T1D, 29.9% (CI 24.6–35.2%) of the participants had hypertension, with higher rates observed among older male patients in association with overweight and obesity and longer diabetes duration, prominently associated with lower insulin sensitivity (Chillarón et al. 2011). In a separate study of 298 youth with T1D (the SEARCH CVD study), lower insulin sensitivity was associated with increasing arterial stiffness, as measured by pulse wave velocity over an average follow-up period of 5 years (Shah et al. 2015). Based on the evidence presented, it is clear that insulin resistance is a significant and potentially modifiable risk factor that may contribute to the adverse cardiovascular outcomes seen in both type 2 and type 1 diabetes.



## Low Birth Weight and Subsequent Insulin Resistance

Low birth weight has been found to be a risk factor for chronic diseases in later life. This association was first described in an epidemiologic study by Barker et al. who identified lower birth weight among men with premature coronary disease (Barker et al. 1989). The birth weight hypothesis proposes that low birth weight, a response to nutritional deprivation within the intrauterine environment, contributes to greater susceptibility to cardiovascular and metabolic diseases in later life, now often called “developmental origins of health and disease,” or DoHAD. Subsequent epidemiologic studies detected modest associations of birth weight to the risk of subsequent cardiovascular disease. In a systematic review of published human studies, Whincup et al. reported that in most populations lower birth weight was associated with increased risk for subsequent development of type 2 diabetes (Whincup et al. 2008). Although insulin resistance is the core metabolic condition underlying metabolic syndrome and type 2 diabetes, the results of clinical investigations to examine the birth weight hypothesis conducted on children have been inconsistent (Li et al. 2001). Variations in obesity, rate of weight gain, secular changes in diet and nutritional patterns, and modest sample sizes explain some of the inconsistent findings (Goran et al. 2003).

Longitudinal studies beginning in early childhood have related recorded birth weight with later childhood outcomes of obesity, blood pressure, and metabolic risk factors. Conditions reported as associated with lower birth weight include maternal hypertensive disorders of pregnancy (Fraser et al. 2013), relative growth rates (Jones et al. 2012), maternal and paternal obesity (Gaillard et al. 2014), and 24-h blood pressure variability in childhood (Wolfenstetter et al. 2012). Prospective studies on perinatal programming that begin in the neonatal or perinatal period on offspring of normal pregnancy are limited. A small but rigorous study on a sample of healthy full-term newborn infants was conducted by Lurbe et al. (2014). Infants were stratified by

birth weight as small (SGA), appropriate (AGA), or large for gestational age (LGA). Blood pressure and weight were measured at 2 days of age, 6 months, 2 years, and 5 years. At 5 years of age a blood sample was obtained for measurement of metabolic parameters. Each birth weight group gained similar amount of weight during each examination interval, and SGA participants remained the smallest and LGA remained the largest. After 6 months, current weight and weight gain were positively associated with birth weight, and there was no association of blood pressure with birth weight. However, at 5 years of age, fasting insulin levels were higher in SGA infants who had become heavy as compared to the AGA and LGA infants who also became heavy. The most striking finding was that SGA infants were insulin resistant, irrespective of their weight status at age 5 years, as measured by HOMA-IR, compared to all AGA and LGA infants. These findings in a sample of healthy infants are consistent with the concept that intrauterine factors related to lower birth weight could induce metabolic programming for relative insulin resistance that is sustained, at least in early childhood, regardless of the weight or weight gain. A variety of potential mechanisms that have been considered to explain fetal programming include the changes in the micro-architecture of various organs, changes in transporters or hormonal levels, and epigenetic modification of DNA. Further research is needed to determine the epigenetic modifications in the perinatal period that may be engaged in fetal programming and the potential for intervention.

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## Genetic Influences on Insulin Resistance

Insulin resistance is a polygenic trait determined by both genetics and environment, especially adiposity. The presence of defective insulin secretion and a tendency towards insulin resistance in non-diabetic family members of patients with T2D highlighted the importance of genetics with heritability estimates of ~38% (Elbein et al. 1999). Subsequent studies in twins and families have shown that the heritability of traits associated

with insulin secretion, such as first-phase insulin secretion by euglycemic clamp, had a higher heritability (0.55–0.58) compared to those of insulin utilization, such as insulin-mediated glucose uptake (Lehtovirta et al. 2000; Poulsen et al. 2005), or surrogate markers of insulin resistance such as HOMA-IR and fasting insulin (Rasmussen-Torvik et al. 2007). One study also identified genetic influences on the insulin response to three different secretagogues (Simonis-Bik et al. 2009). Genome-wide association meta-analyses of 133,010 nondiabetic individuals of European ancestry has identified 53 loci associated with markers of glycemic traits such as fasting insulin, fasting glucose, post-challenge glucose concentrations (Scott et al. 2012). Similar studies in African-American (Chen et al. 2012), Hispanic (Palmer et al. 2010), and Asian (Hong et al. 2014) populations have either replicated the potential importance of these loci or identified new ones. Some of these loci are associated with genes known to influence insulin function such as insulin receptor (*IRS-1*) and glucokinase (*GCKS*) and have a role in T2D, while the function of others such as *klotho* (*KL*), topoisomerase (DNA) I (*TOP1*), etc., remains to be elucidated. In a recent study, Knowles et al. identified a nonsynonymous variant of N-acetyltransferase 2 (*NAT2*) strongly associated with decreased insulin sensitivity independent of BMI, and proved its function in murine adipocyte cell line and in vivo models in mice (Knowles et al. 2015).

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## Treatment of Insulin Resistance

Insulin resistance is intertwined with obesity and other clustered cardiovascular risk factors. Despite the varied definitions of MetS, it is the most commonly used outcome in intervention studies used to assess the effects of treatment. Lifestyle intervention comprising of both diet and physical activity play an essential role in preventing and controlling the development of insulin resistance. Verduci et al. performed a systematic study of 85 Italian children on a 1-year long nutritional behavioral intervention comprising of normocaloric diet by age and sex balanced for the macronutrients distribution with emphasis

on polyunsaturated fats, and fiber along with at least 60 min of daily moderate-to-vigorous intensity physical activity. The investigators observed a significant decrease in both insulin resistance, based on HOMA-IR, and blood pressure level, along with decrease in BMI-z score and increase in HDL (Verduci et al. 2015). Lustig and colleagues provided isocaloric substitution of starch for sugar to restrict fructose intake in 43 children over a 9-day period and observed a statistically significant decrease in the peak insulin levels, insulin AUC during OGTT, and HOMA-IR index with no significant decrease in systolic BP (Lustig et al. 2016).

In a longitudinal, randomized, atherosclerosis prevention trial, Nupponen et al. reported the beneficial effects of a dietary intervention strategy provided since infancy in a cohort of children over 2 decades. Biannual dietary counseling emphasizing a balanced macronutrient composition with emphasis on fiber intake, better-quality carbohydrates, whole grains, low sodium, and polyunsaturated fats over with encouragement of physical activity was provided to families of 540 infants with an equivalent control group (Niinikoski et al. 2014). There was a statistically significant lower prevalence of MetS (6–7% versus 10–14%,  $p < 0.001$ ) in the intervention group along with lower BP and greater insulin sensitivity compared to the control group. (Nupponen et al. 2015; Oranta et al. 2013). Similar benefits of improved insulin sensitivity were also seen with Mediterranean style diet rich in polyunsaturated fatty acids, fiber, flavonoids, and antioxidants with 60% energy from carbohydrates, 25% fat, and 15% protein compared with a standard diet (Velázquez-López et al. 2014). The eating plan for dietary approaches to stop hypertension (DASH) diet is rich in vegetables, fruits, whole grains, low-fat dairy products, along with low sodium intake resulted in decrease in the rates of metabolic syndrome and hypertension in children with no statistical decrease in HOMA-IR index (Saneei et al. 2013). Based on the these data and the importance of maintaining caloric intake to allow for the growth in children, a diet rich in fresh produce, polyunsaturated fats, high fiber,

low sodium, and balanced macronutrients is optimal, starting from early childhood.

Physical activity (PA) is an important lifestyle modification to improve insulin sensitivity. In a systematic review of evidence pertaining to PA and cardiovascular risk factors, Andersen et al. reported that a PA/exercise intervention lasting for at least 30 min, at a frequency of 3 times/week and intensity sufficient to improve aerobic fitness, can be effective in reducing BP in children with hypertension (Andersen et al. 2011). The review reported no association between PA and clustered metabolic risk (MetS) in cross-sectional studies based on self-report. However, in longitudinal studies such as the European Youth Heart Study and studies that used objective methods of assessing physical activity such as accelerometers, a graded association in MetS z-score was seen through all the PA percentiles (Andersen et al. 2011). The reviewers concluded that moderate to vigorous physical activity (MVPA) had to be about 90 min/day to effectively reduce the risk of MetS. Similar findings were noted by Stabelini Neto et al. in a study of 391 Brazilian participants aged 10–18 years. Time spent in MVPA was inversely associated with the continuous risk score for MetS, and the analysis of the ROC curve suggested that the adolescents must perform at least 88 minutes of MVPA per day for the benefit (Stabelini Neto et al. 2014). In a 10-week intensive weight loss camp for obese Danish children, Grønbæk and colleagues observed a marked weight loss (BMI SDS  $-0.56$  to  $-0.72 \pm 0.21$ ) and improvement in BP and insulin sensitivity measured by OGTT and HOMA index. At 12 months after the intervention, the improvements in BMI and BP were lost, but the improvement in insulin sensitivity remained, highlighting the need for long-term interventions (Grønbæk et al. 2012).

Lifestyle interventions are effective, but difficult to maintain. Limited success has been demonstrated in large-scale interventions, especially at the level of the school and community (Jago et al. 2011; Mårild et al. 2015). Pharmacological therapy can be a valuable addition for the treatment of clustering of metabolic effects of hyperinsulinemia and insulin resistance. A number of

randomized controlled trials of varying duration ranging from 2–12 months have demonstrated the benefit of metformin in the treatment of excess weight and metabolic parameters. Freemark et al. observed an improvement in the BMI ( $-0.5$  versus  $0.9$  kg/m<sup>2</sup>,  $p < 0.05$ ), fasting glucose, and fasting insulin in 29 obese adolescents with hyperinsulinemia and a family history of T2D when treated with 500 mg metformin twice daily (Freemark and Bursey 2001). Yanovski and colleagues randomized 100 severely obese children between the ages of 6–12 years to receive 1,000 mg metformin in twice daily dose for 6 months followed by an open label treatment for 6 months. They reported significant decrease in measures of adiposity such as BMI, BMI z-score, and fat mass at the 6 months' time period. They also observed significant decrease in fasting plasma glucose ( $P = 0.007$ ) and HOMA-IR index ( $P = 0.006$ ) in the metformin-treated children compared to those treated with placebo. Gastrointestinal symptoms were significantly more prevalent in metformin-treated children, which limited maximal tolerated dosage in 17% (Yanovski et al. 2011). Similar beneficial results have been seen in other trials of varying duration and doses examining the effects of metformin on the metabolic profile in children with obesity (Atabek and Pirgon 2008; Burgert et al. 2008; Love-Osborne et al. 2008; Luong et al. 2015; Srinivasan et al. 2006). The improvements in insulin resistance, measured predominantly by HOMA-IR or other surrogate markers of insulin resistance, have shown a significant improvement in most of these studies. As many of these studies have documented these improvements with associated weight loss, it is difficult to discern the metabolic benefits from the weight loss versus the isolated effect of metformin on improving insulin sensitivity. A multicentered trial of extended release metformin therapy for 48 weeks followed by an additional 48 weeks of observation did not show a significant improvement in insulin indices or body composition, although a small statistically significant decrease in BMI was seen. It is unclear whether this observation is due to the difference in the administration of the therapy or a true long-term effect (Wilson et al. 2010). Based on the

emerging evidence on the influence of genetic make up on the metabolic benefits of metformin, a recent study reported the influence of polymorphisms in *SLC22A1* on the reduction in adiposity and pharmacokinetics in 30 severely obese children with insulin resistance between the ages of 7–12 years (Sam et al. 2016). There was no difference in the pharmacokinetics based on the genotype, but the change in truncal fat was significantly different between the wild type and the variant genotype. The influence of this and other genetic variants needs further exploration and pave the way for personalized medicine in future.

In a retrospective study of 30 children with MetS who received ACE inhibitor in clinical care, compared to 23 control obese children, Bitkin et al. found no significant differences in the weight, BMI, or the BMI SDS, but significant improvements in the BP and insulin levels along with the HOMA-IR index and lipid profile (Bitkin et al. 2013). No other similar therapeutic studies were identified in the literature at the time of this writing.

## Conclusion and Future Directions

The role of insulin resistance in the development of disease, and interventions to modify it, continue to be an area of intense research. The effect on blood pressure in adolescents by modifications in nutrition, especially with reference to levels of sodium intake and DASH diet in adolescents, are being explored in the NHLBI sponsored CampDASH study (“DASH-Sodium Trial in Adolescents (CampDASH)” 2016). The therapeutic armamentarium of medications for treatment of obesity and its associated metabolic dysfunction is increasing. Liraglutide and other Glucagon-like peptide-1 (GLP-1) analogues have shown a promise in reducing weight, improving insulin resistance, and metabolic profile in adults (Kim et al. 2013, 2014; Pi-Sunyer et al. 2015), resulting in FDA approval for weight loss (“FDA approves weight-management drug Saxenda” 2014). Exploratory work on the role of omega fatty acids and other supplements, and alterations of the microbiome to influence health

and disease profile, appear to be promising. Finally, the increasing emphasis on personalized medicine is driving efforts to identify genetic and epigenetic variations that will likely influence individualized approach to therapy in the future.

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# Monogenic and Polygenic Contributions to Hypertension

# 7

Julie R. Ingelfinger

## Abstract

This chapter provides an overview of the genetics of hypertension, reviewing what is known about rare mendelian forms of hypertension, which can be explained by mutations in single genes, as well as the genetics of primary hypertension. Different approaches that allow discovery of new aspects of the genetics of primary hypertension such as candidate gene approaches, linkage studies, and genome-wide association studies are discussed. It is hoped that this chapter will provide a concise primer for reading the literature in the area of genetics and hypertension. The chapter also provides guidance on patient evaluation and approach.

## Keywords

Monogenic • Polygenic • Familial hypertension • Mendelian • Low-renin hypertension

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## Introduction

More than 17 years have elapsed since the seminal publications in February 2001 that provided the first maps of the human genome [International Human Genome Sequencing Consortium 2001; Venter et al. 2001]. While genes involved in a number of rare, monogenic forms of hypertension have been identified, the genetics of primary hypertension continues to require further elucidation, likely because it has multiple genetic determinants. However, many recently developed tools are available to reveal the genetic aspects of primary hypertension, and a growing number of studies have identified many genetic associations with the condition, which is widely viewed as a polygenic disorder. This chapter discusses both monogenic and polygenic forms of hypertension. We also discuss the current clinical implications of genetic studies and information in our approach to hypertension (Delles and Padmanabhan 2012).

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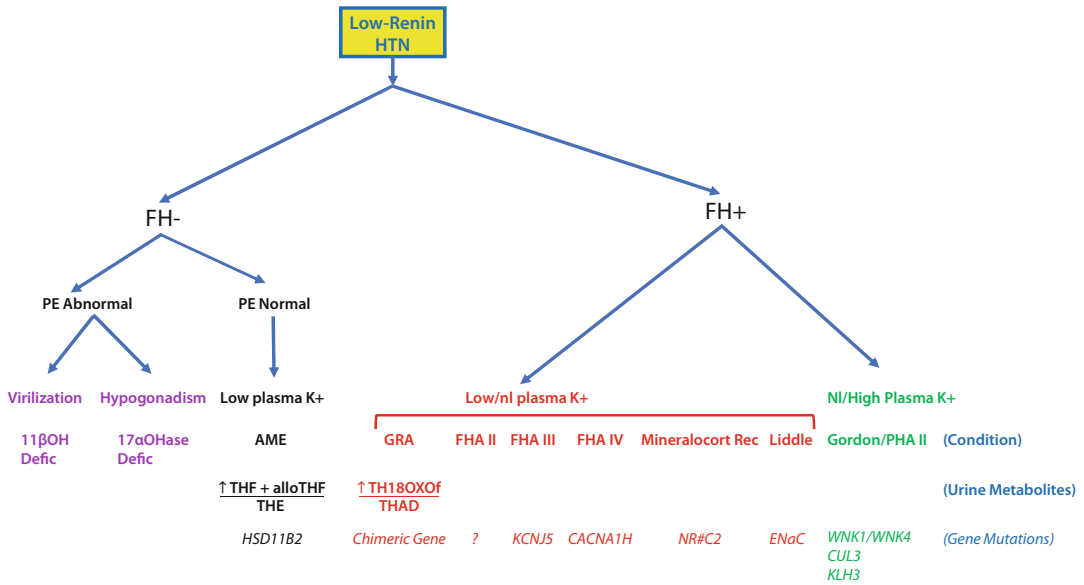
## Monogenic Forms of Human Hypertension

Genes for a number of monogenic forms of human hypertension have been identified via positional cloning [in the past called “reverse genetics”] (Bogardus et al. 2002; Lander and Kruglyak 1995; Wang et al. 1998). In this approach, large kindreds with many affected family members are phenotyped, and the mode of inheritance determined, that is, is the disease autosomal recessive, autosomal dominant, sex linked, and codominant, in its clinical transmission. Subsequently, linkage analysis is performed using highly polymorphic genetic markers such as microsatellite markers that occur widely throughout the genome, evenly

spaced at approximately 10 cM intervals. Since most people (about 70%) are heterozygous, the inheritance of alleles can be traced through large pedigrees. In a successful linkage analysis, a specific chromosomal region in the genome linked to the trait is identified. A LOD [logarithm of the odds] score describes the presence of such a region. The generally accepted LOD score indicating linkage is greater than 3.3 [corresponding to a significance level genome wide of  $4.5 \times 10^{-5}$  (Bogardus et al. 2002)]. Once linkage has been established, a search for known candidate genes in the area of putative linkage commences. A search using additional highly polymorphic markers may also narrow the area of interest, leading to sequences of possible genes within the area.

An increasing number of monogenic forms of hypertension have been identified to date. A number are due to gain-of-function mutations (Dluhy et al. 2002; Lander and Kruglyak 1995; Lifton et al. 2001), most of which involve the renal tubular handling of sodium chloride and/or the overproduction of mineralocorticoids or increased mineralocorticoid activity. Severe hypertension, often from early life – even infancy – is not unusual in such conditions. Clinical hallmarks include apparent volume expansion and suppressed plasma renin activity with variable hypokalemia. An approach to evaluation of those forms of hypertension associated with hypokalemia and suppressed renin activity is shown in Fig. 1 (Yiu et al. 1997).

Gain-of-function mutations in transporters in the distal renal tubule result in hypertension via salt and water retention (Wilson et al. 2001). (While mutations and polymorphisms in the genes of various components of the renin–angiotensin–aldosterone system [RAAS] may lead to excessive renal sodium retention, no single RAAS polymorphism causes monogenic hypertension.) Phenotypically, most monogenic hypertension can be divided into disorders caused by mutations that lead to overproduction of mineralocorticoids or increased mineralocorticoid activity and those that result in abnormalities of



**Fig. 1** Evaluation of patients with hypertension and low plasma renin. Such disorders are either autosomal dominant, generally with a positive family history, or autosomal recessive, generally with a negative family history. Children with glucocorticoid-responsive aldosteronism (GRA), Liddle syndrome, and apparent mineralocorticoid excess (AME) all have normal physical examinations (PE), low plasma renin activity (PRA) or concentration, and hypokalemia. Characteristic urinary steroid profiles and genetic testing distinguish these syndromes. Abbreviations: K<sup>+</sup>, potassium; TH18oxoF/THAD ratio, ratio of urinary 18-oxotetrahydrocortisol (*TH18oxoF*) to urinary

tetrahydroaldosterone (*THAD*), which has a normal of 0–0.4, and in GRA patients >1; THF + alloTHF/THE ratio of the combined urinary tetrahydrocortisol (*THF*) and allo-tetrahydrocortisol (*alloTHF*) to urinary tetrahydrocortisone (*THE*), which has a normal of <1.3, while AME patients are five- to tenfold higher. In addition, *FH* family history, *PE* physical examination, *FHA* familial hyperaldosteronism, *PHA* pseudohypoaldosteronism, *mineralocort.* mineralocorticoid, *nl* normal, *metabs.* metabolites. Related entities are in like colors (Updated and modified from Yiu et al. (1997), with permission)

electrolyte transport, focusing attention on the role of the kidney in hypertension (Table 1) (Lifton et al. 2001; Waddei and Textor 1997). Additionally, some mutations in proto-oncogenes and genes that involve response to hypoxia have been linked to chromaffin tumors (Table 2) (Dluhy 2002b). Information about the most common forms of monogenic hypertension (Melcescu et al. 2012) follows.

### Familial Hyperaldosteronism

There are now four types of familial hyperaldosteronism (Zennaro and Jeunmaitre 2016). Each is reviewed briefly here.

### Glucocorticoid-Remediable Aldosteronism or Familial Hyperaldosteronism Type 1 [OMIM #103900]

Glucocorticoid-remediable aldosteronism (GRA) or familial hyperaldosteronism type 1, an autosomal dominant disorder, is considered the most common type of monogenic hypertension and presents in early infancy in some patients (Biebink et al. 1973; Grim and Weinberger 1980; Miura et al. 1968; New et al. 1973; Oberfield et al. 1981). GRA has been recognized since the 1960s, when Sutherland et al. (1966) and New and Peterson (1967) reported patients with severe hypertension accompanied by suppressed

**Table 1** Some monogenic forms of hypertension

Signs and symptoms	Hormonal findings	Affected tissue/organ	Genetic variants	Comment
<i>Steroidogenic enzyme defects</i>				
Steroid 11 $\beta$ -hydroxylase deficiency	$\downarrow$ PRA and aldo; high serum androgens/urine 17 ketosteroids; elevated DOC and 11-deoxycortisol	Adrenal: zona fasciculata	CYP11B1 mutation [encodes cytochrome P <sub>450</sub> 11 $\beta$ /18 of ZF]; impairs synthesis of cortisol and ZF 17-deoxysteroids	Hypertensive virilizing CAH; most patients identified by time they are hypertensive. Increased BP may also occur from medication side effects
Steroid 11 $\alpha$ -hydroxylase/17,20-lyase deficiency	$\downarrow$ PRA and aldo; low serum/urinary 17-hydroxysteroids; decreased cortisol	Adrenal: zona fasciculata	CYP17 mutation [encodes cytochrome P <sub>450</sub> C17] impairs cortisol and sex steroid production	CAH – male pseudohermaphroditism Female external genital phenotype in males; primary amenorrhea in females
	$\uparrow$ Corticosterone [B] and DOC in plasma; serum androgens and estrogens very low; serum gonadotropins very high	Gonadal: interstitial cells [Leydig in testis; theca in ovary]		
<i>Hyperaldosteronism</i>				
Primary aldosteronism	$\downarrow$ PRA; plasma aldosterone, 18-OH and 18 oxoF; normal 18-OH/aldo ratio	Adrenal adenoma: clear cell tumor with suppression of ipsilateral ZG	Unknown; very rare in children; female:male ratio is 2.5–3:1	Conn syndrome with aldosterone-producing adenoma; muscle weakness and low K <sup>+</sup> in sodium-replete state
Adrenocortical hyperplasia	As above, source of hormone established by radiology or scans	Adrenal: focal or diffuse adrenal cortical hyperplasia	Unknown	As above
Idiopathic primary aldosteronism	High plasma aldo; elevated 18-OHF/aldo ratio	Adrenal: hyperactivity of ZG of adrenal cortex	Unknown	As above
Glucocorticoid-remediable aldosteronism [GRA]	Plasma and urinary aldo responsive to ACTH; dexamethasone suppressible within 48 h; $\uparrow$ urine and plasma 18OHS, 18-OHF, and 18 oxoF	Adrenal: abnormal presence of enzymatic activity in adrenal ZF, allowing completion of aldo synthesis from 17-deoxy steroids	Chimeric gene that is expressed at high level in ZF [regulated like CYP11B1] and has 18-oxidase activity [CYP11B2 functionality]	Hypokalemia in sodium-replete state

Apparent mineralocorticoid excess [AME]	↑ Plasma ACTH and secretory rates of all corticosteroids; nl serum F [delayed plasma clearance]	↑ Plasma F bioact. in periphery [F → E] of bi-dir. 11βOHS or slow clearance by 5 α/β reduction to allo dihydro-F	Type 2 11βOHS mutations	Cardiac conduction changes; LVH, vessel remodeling; some calcium abnormalities; nephrocalcinosis; rickets
<i>Nonsteroidal defects</i>				
Liddle syndrome	Low plasma renin, low or normal K <sup>+</sup> ; negligible urinary aldosterone	Not a disorder of steroidogenesis, but of transport	Autosomal dominant	Responds to triamterene
Pseudohypoaldosteronism II – Gordon syndrome	Low plasma renin, normal or elevated K <sup>+</sup>	Not a disorder of steroidogenesis, but of transport	Abnormality in epithelial sodium transporter, ENaC, in which channel is constitutively active Autosomal dominant	Responds to thiazides
Hypertension exacerbated by pregnancy		Missense mutation of the mineralocorticoid receptor converts antagonists (such as progesterone) to agonists	Abnormality in <i>WNK1</i> or <i>WNK4</i> or in <i>CUL3</i> or <i>KLH3</i> <i>NR3C2</i>	
Mutations in peroxisome-activated receptor gamma		Loss of function mutation results in insulin resistance and hypertension	<i>PPARG</i>	

Adapted and expanded from New et al. (1995)

*Aldo* aldosterone, *PRA* plasma renin activity, *ZF* zona fasciculata, *DOC* 11-deoxycorticosterone, *CAH* congenital adrenal hyperplasia, *18-OHF* 18-hydroxycortisol, *18-OHB* 18-hydroxycorticosterone, *18-OHS* 18-hydroxy-11-deoxycortisol, Compound F, hydrocortisone (also called cortisol). Names of genes are italicized



**Table 2** Mutations associated with pheochromocytomas and paragangliomas

Syndrome	Mutated gene in germ line	Clinical phenotype	Risk of pheochromocytoma (%)
MEN-2A	RET proto-oncogene	Medullary carcinoma of the thyroid, hyperparathyroidism	50
MEN-2B	RET proto-oncogene	Medullary carcinoma of the thyroid, multiple mucosal neuromas, marfanoid habitus, hyperparathyroidism	50
Neurofibromatosis type 1	NF1	Neurofibromas of peripheral nerves, café au lait spots	1
von Hippel–Lindau disease (retinal cerebellar hemangioblastosis)	VHL	Retinal angiomas, CNS hemangioblastoma, renal-cell carcinoma, pancreatic and renal cysts	10–20
Familial paraganglioma syndrome	SDHD, SDHB, SDHC	Carotid-body tumor (chemodectoma)	20 (estimated)

With permission from Dluhy (2002b)

*MEN-2A* multiple endocrine neoplasia type 2A, *MEN-2B* multiple endocrine neoplasia type 2B, *CNS* central nervous system, *SDHD* the gene for succinate dehydrogenase subunit D, and *SDHB* for subunit B, and *SDHC* for subunit C

renin and increased aldosterone secretion that were found to be treatable with dexamethasone. (GRA is listed in the Online Mendelian Inheritance in Man index [OMIM] as #103900 [OMIM can be accessed at <http://www.ncbi.nlm.nih.gov/Omim>]; note that the OMIM numbers for other Mendelian disorders will also be listed for other disorders when available.) The hypertension in GRA is moderate to severe, owing to increased aldosterone secretion driven by adrenocorticotrophic hormone (ACTH).

A chimeric gene containing the 5'-regulatory sequences of 11 beta hydroxylase [which confers ACTH responsiveness] fused with the distal coding sequences of aldosterone synthase causes ACTH rather than angiotensin II or potassium to act as the main controller of aldosterone secretion (Lifton et al. 1992a, b). Both serum and urine aldosterone levels tend to be elevated, though not invariably. The chimeric gene product converts cortisol to 18-hydroxy and 18-oxo metabolites (Ulick and Chu 1982; Ulick et al. 1983; Gomez-Sanchez et al. 1984), which can be detected in urine and are pathognomonic. The elevations of urinary cortisol metabolites TH18oxoF and 18-hydroxycortisol and an

elevated ratio of TH18oxoF/THAD metabolites may distinguish GRA patients from others with AME or Liddle syndrome (Shackleton 1993). However, specific genetic testing, which is both sensitive and specific, has largely supplanted the urinary testing when the condition is suspected.

Not all affected members of GRA families develop hypertension in childhood (Dluhy et al. 2001; Fallo et al. 2004; Kamrath et al. 2011). Dluhy et al. (2001) assessed 20 children in 10 unrelated GRA pedigrees and observed that 16 of the 20 developed hypertension, as early as 1 month of age. However, four children were normotensive. Monotherapy using glucocorticoid suppression or aldosterone receptor and epithelial sodium cotransporter (ENaC) antagonists was sufficient to control BP in half of the hypertensive children, though the others required polypharmacy, and three had uncontrollable hypertension (Dluhy et al. 2001).

Cerebral hemorrhage at an early age (mean age, 32 years) is common in GRA pedigrees. And almost half of reported pedigrees [48%] and 18% of individual GRA patients have been noted to develop cerebrovascular complications (Dluhy et al. 2001; Dluhy 2002a).

### **Familial Hyperaldosteronism Type 2** [OMIM #605635]

This form of hyperaldosteronism, which appears to be autosomal dominant, is distinct from type 1 and is associated with hyperplasia of the adrenal cortex, an aldosterone-producing adenoma, or both (Jeske et al. 2008; Lafferty et al. 2000; Stowasser et al. 1992; Torpy et al. 1998). It has been estimated to be fivefold more common than GRA, and patients often present in childhood or adolescence (Jeske et al. 1998). Dexamethasone fails to suppress the hypertension. The Stowasser group (Jeske et al. 1998) has examined a number of candidate genes within 7p22, many of which involve cell growth. However, to date, no specific mutation has been identified. While *RBaK*, *PMS2*, and *GNA12* have been considered candidate genes on 7p22, none has been shown to be the cause of this condition.

As the genetic cause is not yet identified, diagnosis requires excluding other forms of familial hyperaldosteronism. Once that is accomplished, the aldosterone/PRA ratio is measured in a mid-morning blood sample, being sure that any hypokalemia is corrected and that patient is seated. Further, medications that might affect plasma renin and aldosterone (e.g., ACE inhibitors) should be withdrawn before studies. If the aldosterone/PRA ratio is over 30 (plasma aldosterone measured in ng/100 mL, PRA in ng/mL/h), a fludrocortisone suppression test (FST) to confirm or exclude autonomous aldosterone secretion may be useful (Jeske et al. 1998).

### **Familial Hyperaldosteronism Type 3** [OMIM# 613677]

FH type 3 is very rare and is also called Geller syndrome; it is now known that a heterozygous mutation in the *KCNJ5* gene, which is on chromosome 11q24, leads to familial hyperaldosteronism type III (Choi et al. 2011; Geller et al. 2008; Jeske et al. 2008; Monticone et al. 2012; Stowasser et al. 2011). In this entity, there point mutations in *KCNJ5* change the ion

selectivity of Kir3.4, the inward rectifying potassium channel.

### **Familial Hyperaldosteronism Type 4** [OMIM #617027]

Caused by a heterozygous gain-of-function mutation in the *CACNA1H* gene, another type of FH, classified as type 4, was recently reported by Scholl et al. (2015). *CACNA1H* encodes the voltage-gated calcium channel CaV3.2 in the adrenal glomerulosa. The investigators, in studying 40 patients, all unrelated, all of whom developed hypertension at age 10 years or younger and were found to have low plasma renin activity, high aldosterone levels, and no evidence of adrenal masses, found that five had this underlying cause. In the case of FH-IV, a gain-of-function mutation is present in *CACNA1H* and results in impairment of the involved voltage-gated calcium channel protein (M1549V). The mutant protein causes increased influx of ionized calcium into the glomerulosa cell, which leads to a continuous signal for aldosterone production.

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### **Apparent Mineralocorticoid Excess** [AME] [OMIM # 218030]

Low-renin hypertension, often severe and accompanied by hypokalemia and metabolic alkalosis (Cerame and New 2000), is the hallmark of apparent mineralocorticoid excess [AME], first described in 1977 by New et al. (1977, 1982). Spironolactone is often effective initially, but patients often become refractory to this drug. In AME, 11 $\beta$ -hydroxysteroid dehydrogenase (11 $\beta$ -HSD) deficiency results in hypertension in which cortisol acts as if it were a potent mineralocorticoid. The microsomal enzyme, 11 $\beta$ -hydroxysteroid dehydrogenase, interconverts active 11-hydroxyglucocorticoids to inactive keto-metabolites. Cortisol, as well as aldosterone, has an affinity for the mineralocorticoid receptor. Normally, 11 $\beta$ -HSD is protective, preventing the binding of cortisol to the mineralocorticoid receptor, but in AME, the slower-than-normal metabolism of

cortisol to cortisone results in cortisol acting as a potent mineralocorticoid (New et al. 1977, 1982), while the metabolism of cortisone to cortisol is normal.

Persons with classic AME usually develop symptoms in early childhood, often presenting with failure to thrive, severe hypertension, and persistent polydipsia. Affected patients appear volume expanded and respond to dietary sodium restriction. Plasma renin activity is low, often below the detection limits of laboratory assays. Affected children are at high risk for cardiovascular complications, and some develop nephrocalcinosis and renal failure (Moudgil et al. 2000); early therapy may lead to better outcome. A high cortisol:cortisone ratio in plasma or an abnormal urinary ratio of tetrahydrocortisol/tetrahydrocortisone (THF/THE), in which THF predominates, establishes the diagnosis.

Several variants of AME have been reported, including a mild form in a Mennonite kindred in which there is a P227L mutation in the *HSD11B2* gene (Mercado et al. 1995; Ugrasbul et al. 1999), a coactivator defect with resistance to multiple steroids (New et al. 2001), and hypertension without the characteristic findings of AME in a heterozygous father and homozygous daughter who have mutations in *11βHSD2* (Li et al. 1997). Coeli et al. reported a Brazilian child with a homozygous missense mutation p.R186C in the *HSD11B2* gene (Coeli et al. 2008). Additional mutations within the *HSD11B2* gene have been reported, including one (Pizzolo et al. 2015), in which there is both a mutation in the known gene but epigenetic modification. Genetic testing is indicated when one suspects this disorder.

The hypertension in AME appears mediated through the kidneys, but recent evidence suggests that ultimately, the disorder evolves from one with increased sodium resorption to a vascular form of hypertension (Bailey et al. 2008).

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### Mineralocorticoid Receptor Gain-of-Function Mutation (OMIM #605115)

A novel form of monogenic hypertension due to a gain-of-function mutation in the mineralocorticoid receptor, causing it to remain bound to its

steroid ligands, has also been described. The first known case was a teenage boy with hypertension, who had low plasma renin and aldosterone levels, as well as mild hypokalemia (Geller et al. 2000). In toto, 11 persons in the patient's family had a point mutation, which influences an important binding region of the receptor – a serine at amino acid 810 in the mineralocorticoid receptor is changed to leucine (S810L). In this condition, the gene is on the fourth chromosome at 4q31.2.

Affected persons have refractory hypertension, and women with this mutation have severely elevated BP during pregnancy (Rafestin-Oblin et al. 2003; Kamide et al. 2005). Early death due to heart failure occurred in the index family (Geller et al. 2000).

It appears that the S810L mutation leads to a conformational change in the receptor that heightens the stability of steroid-receptor complexes. The mutation thus results in a steric hindrance, resulting in a bending of the molecule that makes it difficult for known agonists and antagonists to act normally. Some antagonists that cannot act on the normal [“wild type”] receptor work on the mutant receptor: these include RU 486, 5-pregnane-20-one, and 4,9-androstadiene-3,17-dione (Pinon et al. 2004).

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### Steroidogenic Enzyme Defects Leading to Hypertension

Rare autosomal recessive defects in steroidogenesis associated with hypertension were recognized well before the genomic era. Cortisol is normally synthesized under the control of ACTH in the zona fasciculata, while aldosterone is synthesized largely under the influence of angiotensin II and potassium in the zona glomerulosa. Aldosterone synthesis is not normally controlled by ACTH, but if any of the several enzymes that are involved in cortisol biosynthesis is abnormal, the usual feedback loop is interrupted. Consequently, plasma ACTH will increase in an attempt to produce cortisol, and aberrant products will accumulate, some of which lead to hypertension. This is discussed in more detail in ► Chap. 29, “Endocrine Hypertension.”

The inherited defects of steroid biosynthesis – all autosomal recessive – are, as a group, termed congenital adrenal hyperplasia (CAH), and each results in a characteristic clinical and biochemical profile (New and Seaman 1970; New and Levine 1980; New and Wilson 1999). Any enzyme in the pathways of steroidogenesis may contain a mutation; the most commonly affected is 21-hydroxylase. Mutations in 21-hydroxylase are not, however, generally associated with hypertension. Enzyme mutations that are associated with hypertension include [in order of frequency] 11 $\beta$ -hydroxylase > 3 $\beta$ -hydroxysteroid dehydrogenase > 17 $\alpha$ -hydroxylase and cholesterol desmolase. Patients with the 11 $\beta$ -hydroxylase and 3 $\beta$ -hydroxysteroid dehydrogenase defects have a tendency to retain sodium, becoming hypertensive. It is also important to remember that any person with CAH may develop hypertension owing to overzealous replacement therapy.

### 11 $\beta$ -Hydroxylase Deficiency

The mineralocorticoid excess in 11 $\beta$ -hydroxylase deficiency (Krone and Arlt 2009; Mimouni et al. 1985; New and Seaman 1970; New and Levine 1980; New and Wilson 1999; New 2003; White et al. 1991; Zachmann et al. 1971), a form of CAH accompanied by virilization, leads to decreased sodium excretion with resultant volume expansion, renin suppression, and hypertension. Elevated BP is not invariant in 11 $\beta$ -hydroxylase deficiency and most often is discovered in later childhood or adolescence, often with an inconsistent correlation to the biochemical profile (White et al. 1991; Krone and Arlt 2009; Mimouni et al. 1985; New and Seaman 1970; New and Levine 1980; New and Wilson 1999; New 2003; Zachmann et al. 1971). Hypokalemia is variable, but total body potassium stores may be markedly depleted in the face of normal serum or plasma potassium. Renin is generally decreased, but aldosterone is increased.

Therapy of 11 $\beta$ -hydroxylase deficiency should focus on normalizing steroids. Administered glucocorticoids should normalize cortisol and reduce ACTH secretion and levels to normal, thus

stopping oversecretion of deoxycorticosterone (DOC). Hypertension generally resolves with such therapy (New and Seaman 1970). When hypertension is severe, antihypertensive therapy should be instituted until the BP is controlled; such therapy can be tapered later.

Additional mutations can cause this syndrome. For example, a patient with 11 $\beta$ -hydroxylation inhibition for 17 $\alpha$ -hydroxylated steroids but with intact 17-deoxysteroid hydroxylation has been reported (Zachmann et al. 1971). Multiple mutations affecting the *CYP11B1* gene have been described; these include frameshifts, point mutations, extra triplet repeats, and stop mutations (Cerame and New 2000; Curnow et al. 1993; Helmberg et al. 1992; Skinner and Rumsby 1994; White et al. 1991).

### 17 $\alpha$ -Hydroxylase Deficiency

Abnormalities in 17 $\alpha$ -hydroxylase affect both the adrenals and gonads, since a dysfunctional 17 $\alpha$ -hydroxylase enzyme results in decreased synthesis of both cortisol and sex steroids (Biglieri et al. 1966; Mantero and Scaroni 1984; New 1970; Rosa et al. 2007). The enzyme P450c17, encoded by *CYP17A1*, influences both 17 $\alpha$ -hydroxylase (Yanase et al. 1991) and 17,20-lyase activities. Thus, mutations in *CYP17A1* can result in a distinct but subtle syndrome that includes hypertension. Affected persons appear phenotypically female [or occasionally have ambiguous genitalia], irrespective of their genetic sex, and puberty does not occur. Consequently, most cases are discovered after a girl fails to enter puberty (Mantero and Scaroni 1984). An inguinal hernia is another mode of presentation. Hypertension and hypokalemia are characteristic, owing to impressive overproduction of corticosterone [compound B].

For most patients, the increased corticosterone and 11-deoxycorticosterone leads to the typical symptoms. These metabolites are generally excreted into the bile, where they drain into the intestines, and anaerobic bacteria transform them to 21-dehydroxylated forms; in rats, the antibiotic neomycin can block the increased blood pressure.

Such observations suggest that corticosterone, and related  $5\alpha$ -pathway products and also derivatives 11-oxygenated progesterone may be involved in the hypertension in this entity (Morris et al. 2014).

Glucocorticoid replacement is an effective therapy. However, should replacement therapy fail to control the hypertension, appropriate therapy with antihypertensive medication(s) should be instituted to achieve BP control.

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## Mutations in Renal Transporters Causing Low-Renin Hypertension

### Pseudohypoaldosteronism Type II – Gordon Syndrome [OMIM#145260]

Pseudohypoaldosteronism type II or Gordon syndrome was described in the early 1960s and is a rare form of familial hypertension in which there is often marked. Treatment with thiazide diuretics is often successful, as is strict dietary sodium chloride restriction or use of triamterene. Aldosterone receptor antagonists do not correct the observed abnormalities. As thiazides are effective, one would hypothesize that the thiazide-sensitive Na/Cl cotransporter (NCC) would be affected; it turns out to be, but secondarily (Yang et al. 2003). The NCC itself is not abnormal. The use of dDAVP and furosemide has been described as successful.

PHAI genes were mapped to chromosomes 17, 1, or 12 (Mansfield et al. 1997). One kindred was found to have mutations in WNK1 –large intronic deletions that increase WNK1 expression. Another kindred with missense mutations in WNK4, which is on chromosome 17, has been described (Wilson et al. 2003). While WNK1 is widely expressed, WNK4 is primarily expressed in the kidney, localized to tight junctions. WNKs alter the handling of potassium and hydrogen in the collecting duct, leading to increased salt resorption and increased intravascular volume (Wilson et al. 2003).

The pathophysiology of Gordon syndrome is more complex than it first seemed (O’Shaughnessy 2015). The role of the two

serine/threonine kinases that were identified in 2001 as causative – WNK1 and WNK4 – act in a pathway that has other serine/threonine kinases (SPAK and OSR1), and those kinases phosphorylate and activate the Na/Cl cotransporter in the distal tubule, as well as the cotransporters NKCC1 and NKCC2.

Patients with Gordon syndrome also have hyperkalemia, and it is now known that WNK1 and WNK4 normally decrease the cell-surface amounts of the secretory K-channel in the collecting duct, ROMK (Yang et al. 2003).

In addition, it turns out that WNK1/WNK4 mutations are not common among Gordon syndrome families. Recent work shows that other genes may lead to this syndrome – CUL3, which encodes the scaffold protein in a ubiquitin-E3 ligase, Cullin-3 and also KLHL3, which encodes an adaptor protein called Kelch 3.

The genotypes found to date correlate with phenotypes. CUL3 is associated with signs and symptoms very early in life – and profound potassium abnormalities. Indeed, the initial family described by Gordon had very severe hypertension and, recently, was found to have a CUL3 mutation (Glover et al. 2014). The severity and age at first symptoms appears to be severe-to-mild in this order: CUL3 > KLHL3 > WNK4 > WNK1 (Boyden et al. 2012; O’Shaughnessy et al. 2014).

### Liddle Syndrome [OMIM #177200]

Liddle et al. (1963) described the early onset of autosomal dominant hypertension in a family in whom hypokalemia, low renin, and aldosterone concentrations were noted in affected members. Inhibitors of renal epithelial sodium transport such as triamterene worked well in controlling the hypertension, but inhibitors of the mineralocorticoid receptor did not. A general abnormality in sodium transport seemed apparent, as the red blood cell transport systems were not normal (Wang et al. 1981). A major abnormality in renal salt handling seemed likely when a patient with Liddle syndrome underwent a renal transplant and hypertension and hypokalemia resolved post-transplant (Botero-Velez et al. 1994).

While the clinical picture of Liddle syndrome is one of aldosterone excess, aldosterone levels as well as renin levels are very low. Hypokalemia is not invariably present. A defect in renal sodium transport is now known to cause Liddle syndrome. The mineralocorticoid-dependent sodium transport within the renal epithelia requires activation of the epithelial sodium channel [ENaC], which is composed of at least three subunits normally regulated by aldosterone. Mutant beta (SCNN1B) and gamma (SCNN1G) subunits of the ENaC have been identified [both lie on chromosome 16] (Hansson et al. 1995; Shimkets et al. 1994).

Thus, the defect in Liddle syndrome leads to constitutive activation of amiloride-sensitive epithelial sodium channels (ENaC) in distal renal tubules, causing excess sodium reabsorption. Additionally, these gain-in-function mutations prolong the half-life of ENaCs at the renal distal tubule apical cell surface, resulting in increased channel number (Rossier 1997). For a recent review, see Yang et al. (2014).

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### **Pheochromocytoma-Predisposing Syndromes**

A variety of *RET* proto-oncogene mutations and abnormalities in tumor-suppressor genes are associated with autosomal dominant inheritance of pheochromocytomas, as summarized in Table 2 (Aguilar et al. 2001; Baysal et al. 2000; Eng et al. 1995; Erickson et al. 2001; Gimm et al. 2000; Santoro et al. 1995). A number of paraganglioma and pheochromocytoma susceptibility genes inherited in an autosomal dominant pattern appear to convey a propensity toward developing such tumors (Dluhy 2002b). Both glomus tumors and pheochromocytomas derive from neural crest tissues, and the genes identified in one type of tumor may appear in the other (Neumann et al. 1993). For instance, germ-line mutations have been reported both in families with autosomal dominant glomus tumors [as well as in registries with sporadic cases of pheochromocytoma] (Neumann et al. 2002). In addition, other pheochromocytoma susceptibility genes include the proto-oncogene *RET* (multiple endocrine neoplasia syndrome

type 2 [MEN-2]), the tumor-suppressor gene *VHL* seen in families with von Hippel–Lindau disease and the gene that encodes succinate dehydrogenase subunit B (SDHB). For additional discussion, please see ► Chap. 29, “Endocrine Hypertension.”

The genes involved in some of these tumors appear to encode proteins with a common link involving tissue oxygen metabolism (Ackrell 2000; Maxwell et al. 1999; Scheffler 1998). In von Hippel–Lindau disease, there are inactivating [loss-of-function] mutations in the *VHL* suppressor gene, which encodes a protein integral to the degradation of other proteins – some of which, such as hypoxia-inducible factor, are involved in responding to low oxygen tension. Interestingly, the mitochondrial complex II, important in O<sub>2</sub> sensing and signaling, contains both SDHB [succinate dehydrogenase subunit B] and SDHD [succinate dehydrogenase subunit D]. Thus, mutations in the *VHL* gene and SDHB and SDHD might lead to increased activation of hypoxic signaling pathways leading to abnormal proliferation.

In multiple endocrinopathy-2 (MEN-2) syndromes, mutations in the *RET* proto-oncogene lead to constitutive activation [activating mutations] of the receptor tyrosine kinase. The end result is hyperplasia of adrenomedullary chromaffin cells [and in the parathyroid, calcitonin-producing parafollicular cells]. In time, these cells undergo a high rate of neoplastic transformation. It now also appears that apparently sporadic chromaffin tumors may contain mutations in these genes as well.

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### **Hypertension with Brachydactyly [OMIM #112410]**

Hypertension with brachydactyly, also called brachydactyly, type E, with short stature and hypertension (Bilginturan syndrome), was first described in 1973 in a Turkish kindred (Bilginturan et al. 1973). Affected persons have shortened phalanges and metacarpals, as well as hypertension. Linkage studies performed in the 1990s mapped this form of hypertension to a region on chromosome 12p, in the

region 12p12.2–p11.2 (Schuster et al. 1996; Gong et al. 2003).

Patients with this form of hypertension have normal sympathetic nervous system and RAAS responses. In 1996, some abnormal arterial loops were noted on MRI examinations of the cerebellar region. There was speculation that this abnormality could lead to compression of neurovascular bundles that would lead to hypertension (Bähring et al. 1996). Another family, in Japan, also had similar findings, and a deletion in 12p was reported in that family (Nagai et al. 1995).

There are several candidate genes in the region – a cyclic nucleotide phosphodiesterase (PDE3A) and a sulfonylurea receptor, SUR2, which is a subunit of an ATP-sensitive potassium channel. It was hypothesized that there could be “a chromosomal rearrangement between the candidate genes PDE3A/SUR2/KCNJ8 for hypertension and SOX5 for the skeletal phenotypes, separated by several megabases” (summarized in reference (Bähring et al. 2008)). It then appeared, in studies using bacterial artificial chromosomes, that there was an inversion, deletion, and reinsertion in this region. It appears currently that rather than a mutation in a single gene, this form of hypertension is caused by the chromosomal rearrangement.

Recently, it has been shown both in humans and in murine models (Maass et al. 2015; Toka et al. 2015; Boda et al. 2016) that there are causative mutations in phosphodiesterase 3a mutations (*PDE3A*).

## Other Forms of Mendelian Hypertension

In addition, there have been reports of severe insulin resistance, diabetes mellitus, and elevated BP caused by dominant-negative mutations in the gene that encodes the human peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), a transcription factor (Meirhaeghe and Amouyel 2004).

PPAR $\gamma$  is important in the differentiation of adipocytes (reviewed in Meirhaeghe and Amouyel (2004)). Mutations in PPAR $\gamma$  have been linked to a group of symptoms, including

hypertension. Few persons have been described to date with predominant hypertension and have point mutations that are heterozygous (e.g., V290M, R425C, P467L, and F388L) (Agarwal and Garg 2002; Barroso et al. 1999; Hegele et al. 2002; Meirhaeghe and Amouyel 2004; Savage et al. 2003). The affected patients have had marked insulin resistance, then develop type 2 diabetes, and have partial lipodystrophy, as well as hypertension. The finding of these patients has been taken widely as a demonstration of the importance of PPAR $\gamma$  in metabolic syndrome and in blood pressure control, since common polymorphisms appear to be associated with hypertension in the general population.

There has also been a description of hypertension, hypomagnesemia, and hypercholesterolemia due to an abnormality in mitochondrial tRNA. In this case, there is impaired ribosomal binding due to a missense mutation in the mitochondrial tRNA (Wilson et al. 2004).

## When to Suspect Monogenic Hypertension

Table 3 lists those situations in which the astute clinician should consider monogenic hypertension (Dluhy 2002a). These include both clinical and laboratory findings that should point toward further evaluation. Significant among these are a strong family history of hypertension and early onset of hypertension, particularly when the BP is

**Table 3** When to suspect a genetic hypertensive disorder

Patient is a child with marked hypertension, particularly if plasma renin is depressed
Patient is an at-risk member of a kindred with a known monogenic hypertensive disorder (e.g., multiple endocrine neoplasia, glucocorticoid-responsive aldosteronism, etc.)
Patient is a hypertensive child with hypokalemia and first-degree relatives have hypokalemia and/or hypertension
Patient has physical findings suggestive of syndromes or hypertensive disorders (e.g., retinal angiomas, neck mass, or hyperparathyroidism in patient with a pheochromocytoma)

Adapted from Dluhy (2002a)

difficult to control within the family. Low plasma renin activity, along with hypokalemia, should also point toward the possibility that a defined form of hypertension may be present.

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## Non-Mendelian, Polygenic Hypertension

The genetic contribution to a prevalent condition such as primary[essential] hypertension is widely considered to involve multiple genes and is thus termed polygenic. The possibility for determining the genes that are involved seems far more feasible in the current genomic era, yet clear identification has proved elusive, in part because BP is a continuous variable, and the contribution of any one gene appears to be small. Relevant background for considering the genetic factors predisposing toward hypertension follows (Cabrera et al. 2015; Wei et al. 2017).

### Experimental Hypertension as a Tool to Investigate Polygenic Hypertension

Many studies in inbred experimental animals, mainly rats and mice, have aimed to identify genes controlling BP (see ► Chap. 46, “Hypertensive Models and Their Relevance to Pediatric Hypertension”). In the 1980s, it was estimated that five to ten genes control BP (Harrap 1986). In 2000, Rapp summarized available research and estimated that 24 chromosomal regions in 19 chromosomes were associated with hypertension in various rat strains (Rapp 2000). A recent review by (Delles et al. 2009) notes that candidate QTLs (quantitative trait loci) have been identified on nearly every chromosome. Studies using inbred rat strains, however, did not identify polygenes and their associated alleles (Doris 2002).

A large number of chromosomal regions and some candidate genes have also been suggested from experimental studies in mice. For example, targeted gene deletion studies have shown an effect on BP in more than a dozen genes, among which are endothelial nitric oxide synthase, insulin receptor substrate, the dopamine receptor,

apolipoprotein E, adducin-alpha, the bradykinin receptor, and the angiotensin type 2 receptor, as well as other members of the RAAS (Cvetkovic and Sigmund 2000).

Genetic manipulation in mice has been successful in exploring contributions of various candidate genes (reviewed in Gordon and Ruddle (1983)), most notably those of the RAAS through two approaches, overexpression of a given gene [with “transgenic” animals (Rapp 2000) and deleting gene function [with “knockouts”]. An additional approach is to use gene targeting in embryonic stem [ES] cell cultures (Capecchi 1989; Evans and Kaufman 1981; Jacob et al. 1991).

Inbred strains rather than transgenic or knockouts have led to important findings (Hilbert et al. 1991; Jacob et al. 1991; Lalouel et al. 2001; Saavedra 2009). A number of studies, notably those of Jacob et al. (1991) and Hilbert et al. (1991), found linkage in a rat model of hypertension that pointed to the angiotensin-converting enzyme (ACE) gene as important in determining hypertension. Since those reports of more than 25 years ago, a large number of clinical studies have suggested a link between ACE polymorphisms in humans and hypertension. See commentaries on the value of studies in the rat model (Delles et al. 2009; Saavedra 2009).

### Human Hypertension

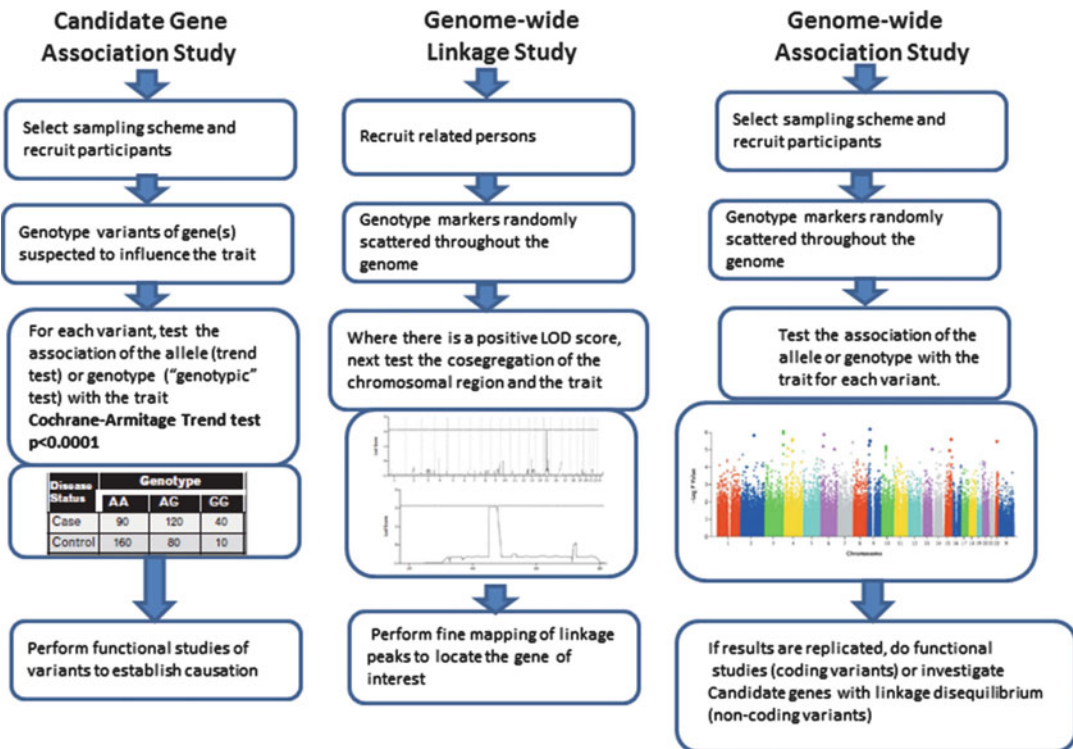
A variety of studies have pointed to a link between human hypertension and genes of the RAAS (summarized in Lalouel et al. 2001; Zhu et al. 2003). However, in common diseases such as hypertension, it may be more productive to consider susceptibility alleles rather than disease alleles per se. Furthermore, some people carrying a particular susceptibility allele may not have the disease, either because they have not encountered the environmental exposure that causes the condition to develop or because they lack another allele [or alleles] that are needed to cause a given clinical problem. Because there are multiple potential interactions, and susceptibility alleles are generally common, following a given allele



through pedigrees is difficult. In such a circumstance, segregation analysis is difficult, particularly if a given susceptibility allele has a small effect. Indeed, to date, linkage has been reported on most chromosomes in humans (Binder 2007; Caulfield et al. 2003; Cho et al. 2009; Ehret et al. 2008; Harrap 2003; Hamet and Seda 2007; Hong et al. 2009; Izawa et al. 2003; Krushkal et al. 1999; Levy et al. 2000, 2007; Martinez-Aguayo and Fardella 2009; Newton-Cheh et al. 2009; Pan et al. 2015; Pankow et al. 2000; Perola et al. 2000; Province et al. 2003; Rice et al. 2000; Sharma et al. 2000; International SNP Map Working Group 2001; Wang et al. 1998; Wellcome Trust Case Control Consortium 2007; Xu et al. 1999).

While linkage analysis may constitute an initial step (Bogardus et al. 2002; Delles and Padmanabhan 2012; Lander and Kruglyak 1995; Wang et al. 1998), it is not as powerful a tool in

polygenetic conditions as it is in Mendelian diseases, because many people without the disease may carry the susceptibility allele. Using affected siblings [sib pairs] may be helpful to gain more understanding of the possible genetics (see Fig. 2). Siblings who are both affected with a given problem such as hypertension would be anticipated to share more than half their alleles near or at the susceptibility locus, and the chance of this occurrence is then calculated (Bogardus et al. 2002; Delles and Padmanabhan 2012; Lander and Kruglyak 1995; Wang et al. 1998). A LOD score of greater than 3.6 is taken as evidence of a linked locus, which is often very large (in the range of 20–40 cM). Once a putative linkage is confirmed in a replicate study, finer mapping can be performed to hone in on the genetic region that contains the putative gene. This is done via linkage disequilibrium or association testing between disease and genetic markers,



**Fig. 2** Study designs used to dissect the genetic architecture of common complex traits. This figure shows the flow of studies that utilize candidate gene approaches, genome-wide linkage studies and genome-wide association studies

(After Simino et al. (2012), with permission. Insets for genome-wide linkage and genome-wide association studies are from Graphic Arts, the New England Journal of Medicine, with permission)

often with single-nucleotide polymorphisms (SNPs). SNPs occur roughly every 1,000 base pairs and lend themselves to automated testing. Using SNPs, a broad region (10–40 cM) can be narrowed to a far smaller region of roughly  $1 \times 10^6$  base pairs (Wang et al. 1998; International SNP map working group 2001).

Genome-wide screens of the human genome aiming to discover hypertension genes have suggested many loci of interest (Cabrera et al. 2015; Harrap 2003; Province et al. 2003). These genome-wide screens have included subjects with diverse phenotypes and ethnicity; furthermore, selection criteria have varied. The numbers and composition of families have ranged from single, large pedigrees to more than 2,000 sib pairs from 1,500 or so families (Harrap 2003). Using genomic scan data from four partner networks, the US Family Blood Pressure Program (FBPP) (Province et al. 2003) sought to use phenotypic strategies that reflect the ethnic demography of the USA. A 140–170 cM region of chromosome 2 was linked to hypertension in several populations – Chinese sibling pairs (Xu et al. 1999) and Finnish twins (Perola et al. 2000), as well as a discordant sibling-pair screen. Recently Caulfield et al. phenotyped 2,010 sib pairs drawn from 1,599 families with severe hypertension as part of the BRIGHT study [Medical Research Council BRITish Genetics of Hyper Tension Study] and performed a 10 cM genome-wide scan (Caulfield et al. 2003). Their linkage analysis identified a locus on chromosome 6q with a LOD score of 3.21 and genome-wide significance of 0.042. However, this locus is at the end of chromosome 6, and the end of a chromosome may generate errors; thus, caution is required in drawing conclusions from these findings. The Caulfield group also found three other loci with LOD scores above 1.57 (Caulfield et al. 2003). One of these loci was the same as that found in the Chinese and Finnish studies (Caulfield et al. 2003).

There have been further genome-wide association studies (GWAS) concerning hypertension reported (Hamet and Seda 2007; Martinez-Aguayo and Fardella 2007; Pan et al. 2015; Sober et al. 2009). In 2007, Levy et al. used an Affymetrix 100k chip platform and performed a

GWAS with the Framingham cohort, yet the initial analysis did not find significance for any single gene (Levy et al. 2007). Using the Wellcome Trust Case Control Consortium [WTCCC] and an Affymetrix 500k chip, another GWAS was reported in 2007, and it, too, did not reach genome-wide significance for any gene (Wellcome Trust Case Control Consortium 2007). However, a study in which the subjects were from the Korean general population most recently reported genome-wide significance, though a very small effect for the ATPase,  $\text{Ca}^{++}$ -transporting, plasma membrane 1 (*ATP2B*) gene (Cho et al. 2009). These rather disappointing results from GWAS studies on hypertension are discussed to indicate the complexity of primary hypertension.

Two consortiums have reported some more encouraging results. The Global BPgen group examined 2.5million genotyped or imputed SNPs in 34,433 persons of European background and found eight regions that reached genome-wide significance. These regions were associated with hypertension and lie in close proximity to genes for *CYP17A1*, *CYP1A2*, *FGF5*, *SH2B3*, *MTHFR*, *ZNF652*, and *PLCD3* and to the chromosome 10 open reading frame 107 (*c10orf107*) (Newton-Cheh et al. 2009). Further, the so-called CHARGE consortium (Levy et al. 2009) looked at 29,136 participants and studied 2.5million genotyped or imputed SNPs; they reported significant associations with hypertension for ten SNPs and with systolic BP for 13 SNPs and for diastolic BP with 20 SNPs. Their findings plus those of Global BPgen were then subjected to a meta-analysis, and this led to findings of genome-wide significance for a number of genes associated with elevated BP or with systolic or diastolic BP (Newton-Cheh et al. 2009). These included the *ATP2B* gene, as well as *CYP17A1* (steroid 17- $\alpha$ -phamonoxygenase), *CSK-ULK3* (adjacent to c-src tyrosine kinase and unc-51-like kinase 3 loci), *TBX3-TBX5* (adjacent to T-box transcription factor *TBX3* and T-box transcription factor *TBX5* loci), *ULK4* (unc-51-like kinase 4), *PLEKHA7* (pleckstrin homology domain containing family A member 7), *SH2B3* (*SH2B* adaptor protein 3), and *CACNB2* (calcium

channel, voltage-dependent, beta 2 subunit) (Newton-Cheh et al. 2009).

## Candidate Genes

Another approach in assessing polygenic hypertension is to use candidate genes – genes that already have a known or suspected role in hypertension – that are present near the peak of observed genetic linkage (Wei 2016; Sober et al. 2009). If the full sequence of the candidate gene is known, then it is relatively easier to go forward.

In the Caulfield study (Caulfield et al. 2003), for example, there are a number of candidate genes that are within the linkage analysis-identified areas on chromosomes 2 and 9. Genes that encode serine-threonine kinases, STK39, and STK17B are on chromosome 2q; PKNBETA, a protein kinase, is on chromosome 9q; G protein-coupled receptors on chromosome 9 – GPR107 9q and GPR21 on 9q33; and on 2q24.1 there is a potassium channel, KCNJ3.

Use of microarrays to identify differential expression of expressed sequences in tissues from affected and unaffected persons has become common. These arrays are available either as full-length cDNAs or as expressed sequence tags (ESTs).

## Candidate Susceptibility Genes

A number of genes have become candidates as susceptibility genes, particularly those of the RAAS. A number of such genes were associated with hypertension and cardiovascular regulation in the pre-genomic era. Many associations have been described or imputed, including not only members of the RAAS but many other genes. For example, Izawa et al. (2003) chose 27 candidate genes based on reviews of physiology and genetic data that looked at vascular biology, leukocyte and platelet biology, and glucose and lipid metabolism. They then also selected 33 SNPs of these genes, largely related in promoter regions, exons, or spliced donor or acceptor sites in introns

and looked at their relationship to hypertension in a cohort of 1,940 persons. They found that polymorphisms in the CC chemokine receptor 2 gene were associated with hypertension in men and the TNF-alpha gene was associated with it in women (Krushkal et al. 1999). In a GWAS in African Americans, Adeyemo et al. (2009) suggested that pathway and network approaches might be helpful in identifying or prioritizing various loci.

## Variants or Subphenotypes

If a particular variant of a complex disease is clinically distinct, then analysis of so-called subphenotypes via positional cloning may be potentially illuminating (Bogardus et al. 2002; Delles and Padmanabhan 2012; Lander and Kruglyak 1995; Levy et al. 2000; Xu et al. 1999). In such an instance, there may be fewer susceptibility genes involved. However, subphenotypes may be difficult to study, as the physiology involved may be intricate. An example would be salt-sensitive hypertension (Levy et al. 2000). In order to study subjects, it is necessary to perform careful metabolic studies that confirm the subphenotype [hypertension with salt sensitivity] and also is standard during testing.

Another approach worth mentioning is that of genome-wide admixture mapping – mapping by admixture linkage disequilibrium (MALD), which is used to detect genes in populations that are mixed, for example, where one group's ancestors have more of a given disease than another group (Simino et al. 2012). Using a moderate number single-nucleotide polymorphisms (SNPs), this method determines regions in the genome that contain more SNPs from one ancestral group as compared to the others. Then honing down on the area, genes of interest may be found. This approach is very appealing as a means by which to study hypertension in African Americans (Kopp et al. 2008; Genovese et al. 2010). For example, MALD was used to find a linkage peak in persons with African ancestry, which has turned up two apolipoprotein L1 (APOL1) variants in the coding region, as well as an adjacent

area in the myosin heavy chain 9 gene (MYH9), which are associated with focal segmental glomerulosclerosis and hypertension.

## Present Implications for Pediatric Hypertension

A search for monogenic forms of hypertension is clearly indicated in an infant, child, or teenager with elevated BP and history or signs compatible with one of these diagnoses. If a child is found to have one of the rare forms of monogenic hypertension, there will be specific therapy. Few data, however, exist to guide the clinician in terms of the roles polygenic hypertension in children at the present time. Current approaches, summarized in Fig. 2 and in recent reviews (Delles et al. 2010; Braun and Doris 2012; Hiltunen and Kontula 2012; Cowley et al. 2012; El Shamieh and Visvikis-Siest 2012; Padmanabhan et al. 2012; Simino et al. 2012; Cooper-DeHoff and Johnson 2016; Luft 2017), would still indicate that the concept of a complex set of interactions leads to most cases of hypertension.

There is no doubt that varied genetic mechanisms that lead to primary hypertension remain to be delineated. In the future gene–environment interactions, pathways that involve multiple gene products, as well as epigenetic phenomena, will be explored. Ultimately, there may be pharmacogenetic approaches by which therapy for hypertension may be individualized (Table 1).

## Cross-References

- ▶ [Endocrine Hypertension](#)
- ▶ [Hypertensive Models and Their Relevance to Pediatric Hypertension](#)

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## Abstract

A suboptimal perinatal environment can adversely influence gamete, embryonic, fetal, and infant development, setting in motion a train of events that increases the risk of hypertension and cardiovascular disease throughout life. This chapter summarizes the evidence linking an adverse maternal environment to developmental plasticity, in which the fetus adapts to the prevailing environmental conditions, subsequently altering the adult phenotype. Early studies linked low birth weight to the programming of high blood pressure. However, it is now evident that altered fetal development can also occur independently of low birth weight. Thus, the health implications of the maternal environment are much greater than predicted by the proportion of babies suffering growth restriction. We discuss

both the stimuli and mechanisms that drive the perinatal programming of arterial pressure. We will consider kidney structure and function as a primary determinant of arterial pressure, as well as vascular, cardiac, and neural adaptations. Finally, therapeutic options to prevent, limit, or reverse these adverse consequences of a challenging start to life are explored.

## Keywords

Maternal environment • Maternal nutrition • Glucocorticoids • Developmental programming • Low-birth weight • Arterial pressure • Kidney • Nephron number • Perinatal supplements

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## Introduction

Hypertension increases the risk of heart disease, stroke, and kidney failure, which together are the major causes of death globally. Worldwide, approximately 40% of adults over the age of 25 years have hypertension. A person's blood pressure phenotype is not only determined by his or her genetic makeup but is also substantially influenced by prenatal and postnatal environmental factors. To a large extent, the present global hypertension epidemic is driven by under- and overnutrition and sedentary life style. However, life in utero is now recognized as an environment during which adverse factors can also influence fetal development to the detriment of future health.

Perturbations in the maternal milieu during pregnancy have been associated, in the exposed child, with subsequent hypertension and cardiovascular disease in adulthood. Moreover, it has been demonstrated that the environment in early childhood and, more recently, the maternal environment around the time of conception, not only influence oocyte development, but also impact health in adulthood. Finally, evidence demonstrates that such programming effects can be trans-generational, transferring to the child from the mother, priming the child for future health issues and crossing to successive generations. This chapter considers epidemiologic and experimental evidence demonstrating the effects of various environmental influences on the development of the fetus and the subsequent programming of hypertension in adulthood.

## Linking the Maternal Environment to Low Birth Weight and Cardiovascular Disease

A series of landmark retrospective studies in the 1980s demonstrated an association between coronary heart disease and infant mortality (Barker and Osmond 1986) and, later, between stroke (Barker and Osmond 1987), hypertension (Barker et al. 1989), and birth weight. These retrospective studies made possible by the detailed birth records kept in the United Kingdom in the early 1900s, linked a suboptimal start to life, as indicated by a low birth weight, to cardiovascular disease in adulthood. Such observations led to the hypothesis that adult disease has developmental origins – in other words, that an adverse environment during development (either in utero or in the early postnatal period) programs changes in fetal or neonatal development, rendering a person at greater risk of developing disease in adulthood (Law and Barker 1994).

Following these initial studies, clinical records across the globe were mined for similar information. The Dutch Hunger Winter study (a study of children born during a famine in the Netherlands during the Second World War) demonstrated that malnutrition during pregnancy was linked to hypertension in adults >55 years of age (Stein et al. 2006). The Jerusalem Perinatal Follow-up study demonstrated that high prepregnancy maternal body mass was associated with hypertension in adults of ~30 years of age (Hochner et al. 2012). More recent prospective studies, though with shorter follow-up than the initial studies of Barker et al. (3–20 years of age), have also related increased arterial pressure in children to maternal factors during pregnancy: weight gain (Filler et al. 2011), smoking (Oken et al. 2005), vitamin D deficiency (Williams et al. 2013), preeclampsia (Fraser et al. 2013), and short-term breastfeeding (Hosaka et al. 2013). Overwhelmingly, in these studies the babies with greater risk had lower birth weights (<2.5 kg). Thus, there is strong epidemiologic evidence supporting the association of an adverse maternal environment, altered fetal development causing low birth

weight, and increased risk of hypertension and cardiovascular disease in adulthood (Fig. 1).

To demonstrate causation, and to understand the underlying mechanisms, it was necessary to perform studies in animal models in which the maternal environment was compromised. Low birth weight and fetal growth restriction most commonly result from inadequate maternal nutrient uptake and/or poor placental function. To model these conditions, experimental studies have utilized the approach of reducing total calorie or macronutrient (protein) intake throughout pregnancy or during specific periods within gestation. Additionally, methods to limit uterine perfusion have been employed to mimic a common cause of fetal growth restriction in humans.

## Impact of the Maternal Environment

### Maternal Nutrition

#### Calorie Restriction

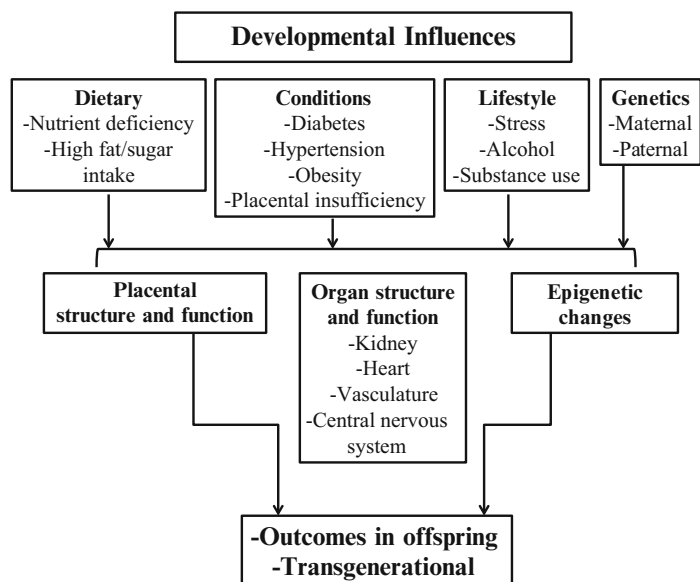
Reduced access to food throughout pregnancy, resulting in a decrease in global caloric intake, has in many, but not all, experimental studies been shown to cause low birth weight and increased arterial pressure in adulthood (Brennan

et al. 2006; Woods 2007). Such studies also identified critical periods in development when offspring are more susceptible to food restriction and indicated that the effects vary with the sex of the offspring.

In rats, global food restriction (30% of control intake) from day 0 to 18 of pregnancy (term = 21 days) resulted in elevated blood pressure in male offspring from postnatal day 60 and in female offspring from postnatal day 100 (Ozaki et al. 2001). However, in another study, 50% food restriction from day 0 to 20 of gestation in the rat resulted in a blunted rise in nocturnal blood pressure, thus overall resulting in lower 24-h blood pressure in male offspring at 12 weeks of age (Brennan et al. 2008). In still another study, 50% food restriction throughout gestation in the rat resulted in an increase in systolic blood pressure in 150-day-old male offspring, and this increase in blood pressure was prevented in offspring treated with growth hormone between postnatal days 3 and 21 (Gray et al. 2013).

The importance of the postnatal environment in programming of hypertension was also demonstrated when food restriction in rats was induced, not in the mother, but in the offspring from postnatal day 3 to 90; in that study increased blood pressure and heart rate were observed in offspring

**Fig. 1** Overview of maternal influences on the development of the fetus leading to adult hypertension



at 3 months of age (de Belchior et al. 2012). In sheep, 50% reduction in maternal food intake from day 115 of gestation (term = 150 days) increased arterial pressure in the 115- to 125-day-old fetal sheep (Edwards and McMillen 2001). However, 50% food restriction earlier in gestation (between gestational days 28 and 80) lowered resting systolic and diastolic blood pressure in offspring at age 6 months (Gopalakrishnan et al. 2005). In another study in sheep, maternal food restriction between gestational days 1 and 30 resulted in offspring blood pressure similar to that of control offspring at 1 year of age (Gardner et al. 2004). However, food restriction in ewes between gestational days 0 and 95 resulted in offspring with higher blood pressure than that of control offspring at 3 years of age (Gopalakrishnan et al. 2004).

Taken together, these studies in experimental animal models demonstrate that maternal undernutrition causes low birth weight and increased arterial pressure in adulthood, reinforcing the same association demonstrated in human epidemiologic studies. In addition, these findings indicate that the more severe the food restriction, the worse the outcome and that males may be more adversely affected than females. This is in agreement with other literature that indicates that females, at least prior to menopause, are protected against hypertension and cardiovascular disease. It also suggests that there are developmental windows, possibly coinciding with organogenesis, during which the fetus is more sensitive to nutritional insults. Finally, this work also demonstrates that the early postnatal period is also an important developmental timepoint at which future risk of hypertension may be entrained.

### **Protein Restriction**

Dietary protein restriction during pregnancy has been commonly utilized to examine the effects of nutrient deficiency on offspring health. In such models, animals receive a protein-deficient diet rendered isocaloric by the addition of a carbohydrate, in order to allow differentiation between the actions of protein vs. calorie restriction. Langley-Evans et al. (1999) demonstrated that dietary protein restriction (8% casein compared with 20%

control, isocaloric) in female Wistar rats from day 1 of gestation to term resulted in elevated systolic blood pressure in offspring. Woods et al. (2004) demonstrated that severe protein restriction (5% casein, isocaloric) in pregnant Sprague Dawley rats resulted in an increase in blood pressure in both male and female offspring aged 20 weeks. However, this effect was only observed if protein restriction occurred throughout gestation or during the second half of gestation (days 11–22), but not if protein restriction occurred in the first half of gestation (day 1–11). Vehaskari et al. (2001) demonstrated an increase in blood pressure in both male and female rat offspring from 8 weeks of age using similar maternal protein restriction (6% casein, isocaloric) between day 12 of gestation and term. However, more modest maternal protein restriction (8.5% casein, isocaloric) for all of gestation caused an increase in blood pressure in male but not female rat offspring (Woods et al. 2005). Interestingly, modest dietary protein restriction (9% casein, isocaloric) in the rat from before pregnancy until the end of lactation had no effect on blood pressure of the male offspring (Zimanyi et al. 2004). Moreover, maintenance of these offspring from protein-restricted dams on the low-protein diet after weaning resulted in hypotension in male offspring (Hoppe et al. 2007). It has been hypothesized that inconsistencies in outcomes between studies may reflect subtle variations in the macronutrients contained within each diet and/or differences in the genetic background of the rat strains employed. However, the weight of evidence supports the findings of the Dutch Winter Famine study (Stein et al. 2006) and demonstrates that undernutrition at different stages of fetal/neonatal development can differentially affect blood pressure outcomes in the child/adult.

### **Placental Insufficiency**

Abnormal placental function can also restrict fetal nutrient delivery and is the most common cause of fetal growth restriction in women from developed countries. Studies of uteroplacental insufficiency in the rat and sheep result in fetal growth

restriction and low birth weight (Louey et al. 2003; Schreuder et al. 2006; Wlodek et al. 2008). Utero-placental insufficiency induced by bilateral ligation of uterine vessels on day 18 of gestation in rats results in hypertension in adult male but not female offspring (Schreuder et al. 2006; Wlodek et al. 2008). Similarly, placental insufficiency induced by reduction in uterine perfusion pressure in rats resulted in elevated blood pressure in male but not female offspring (Alexander 2003), with the age-related increase in blood pressure being accelerated in growth-restricted male offspring (Dasinger et al. 2016a). However, in sheep, placental insufficiency induced by umbilico-placental embolization in late gestation resulted in growth restriction, but the offspring were hypotensive at 2 years of age (Louey et al. 2003).

A reduction in uterine perfusion pressure has been shown to cause gestational hypertension in the rat (Li et al. 2012) and mouse (Intapad et al. 2014). In the rabbit, maternal hypertension induced by renal wrapping (two-kidney-1-wrap hypertension, in which one kidney is literally wrapped with cellophane, also called the Page kidney) resulted in an increase in blood pressure in female but not male offspring (Denton et al. 2003; McArdle et al. 2010). The maternal hypertension in these studies in rabbits was associated with a reduction in uterine blood flow (McArdle et al. 2010).

In human cohort studies, both hypertension during pregnancy and preeclampsia have been associated with development of high blood pressure in offspring. For example, in the AVON Longitudinal Study of Parents and their Children (ALSPAC), a large UK study (~4600 mother-child pairs), a positive association between gestational hypertension and blood pressure in the offspring was observed in the children at age 9–12 years (Lawlor et al. 2012). In the 1986 Northern Finland Birth cohort study, significant elevations in blood pressure were observed in 16-year-old children of mothers who had gestational hypertension compared with children of normotensive mothers (Miettola et al. 2013). Together such studies, in addition to showing that placental insufficiency can program arterial pressure in

offspring, also suggest that hypertension of non-genetic origin can be transferred across generations.

## Maternal Obesity

Obesity in pregnancy is associated with numerous maternal complications, including the development of gestational diabetes, miscarriage, and delayed onset of labor. Maternal obesity affects the fetus and can result in either large for gestational age or growth-restricted offspring. One meta-analysis demonstrated that a higher maternal prepregnancy body mass index (BMI) increased the risk of having large for gestational age babies, which were also at increased risk of obesity later in life (Yu et al. 2013). However, a caveat to the interpretation of many epidemiological studies is the confounding presence of obesity in the offspring. Mamum et al. (2009) reported an association between blood pressure in progeny at 21 years of age and maternal gestational weight gain following adjustment for offspring BMI. Catalano et al. (2009) demonstrated that maternal prepregnancy BMI  $\geq 30$  kg/m<sup>2</sup> was associated with greater body fat percentage, waist circumference, higher systolic blood pressure, insulin resistance, and greater plasma triglyceride and leptin levels in children at 8 years of age. In the Jerusalem cohort study, consisting of 1400 young adults, higher maternal prepregnancy BMI, independent of gestational weight gain was associated with higher offspring BMI, systolic and diastolic blood pressure, plasma insulin, and triglycerides levels (Hochner et al. 2012). However, in the same Jerusalem cohort study, gestational weight gain independent of maternal prepregnancy BMI was positively associated with offspring adiposity and waist circumference, but the association with cardiovascular risk disappeared once adjustments were made for offspring BMI (Hochner et al. 2012). In contrast, in the Amsterdam Born Children and their Development (ABCD) study, consisting of 3074 women, a positive association between prepregnancy maternal BMI and offspring blood pressure (systolic and diastolic) at 5–6 years of age was reported and that association

remained significant, even when childhood BMI was factored into the analysis (Gademan et al. 2013).

In laboratory studies, the impact of maternal obesity on offspring blood pressure has mostly been investigated in rodents using the approach of maternal overnutrition (Taylor et al. 2004). Prepregnancy obesity has been induced by feeding rodents diets high in fat with addition of simple sugars, the so-called “cafeteria-style” diet, which causes weight gain. A high fat diet in rats initiated from 5 weeks before pregnancy and through lactation resulted in a significant increase in arterial pressure in juvenile (30 days old) male and female offspring (Samuelsson et al. 2010). The increase in blood pressure in this model was also reported in the absence of increased adiposity and hyperinsulinemia (Nivoit et al. 2009). In contrast, in mice male and female offspring of dams that were placed on an obesogenic diet 6 weeks prior to mating, throughout pregnancy and during lactation, were hyperphagic between 4 and 6 weeks of age and hypertensive by 3 months of age (Samuelsson et al. 2008). An increase in offspring blood pressure of mothers fed a high-fat diet has also been demonstrated in rabbits (Prior et al. 2014). Thus, not only undernutrition but also maternal overnutrition (or increased maternal BMI) adversely influences fetal development, increasing future risk of cardiovascular disease.

## Maternal Diabetes

Gestational diabetes is commonly observed in pregnancies complicated by obesity. Krishvani et al. (2010) examined the effects of both maternal and paternal diabetes on health of offspring. It was observed that maternal diabetes was associated with increased systolic blood pressure, adiposity, and insulin resistance in female offspring, but only increased insulin resistance in male offspring. In contrast, paternal diabetes alone was associated with increased adiposity in female offspring and with insulin resistance in male offspring, but these effects were weaker than those observed with maternal diabetes (Krishnaveni et al. 2010). Maternal diabetes has been linked to

raised systolic blood pressure and increased plasma biomarkers of vascular dysfunction in their children at age 6–13 years (West et al. 2011). In a meta-analysis examining blood pressure in children born to diabetic mothers, male offspring had significantly higher systolic and diastolic blood pressure than offspring of non-diabetic mothers, whereas female offspring had blood pressure similar to controls (Aceti et al. 2012). These findings provide some data to suggest that maternal metabolic status may influence perinatal programming of arterial pressure.

Experimental studies in animal models support the concept that maternal metabolic status may influence arterial pressure in offspring. Wichi et al. (2005) demonstrated in rats that litter size was reduced, blood glucose levels were elevated prior to weaning, and systolic blood pressure was increased at 8 weeks of age in offspring of diabetic dams. More recently, studies in both rat (Franca-Silva et al. 2016) and mouse (Chen et al. 2010) offspring of diabetic dams demonstrated that adult systolic blood pressure was increased in association with glucose intolerance compared with offspring of nondiabetic dams. Moreover, these phenotypes were prevented following maternal insulin treatment. In pregnant rats in which diabetes was induced late in gestation (from day 13), an increase in blood pressure from 2 months of age was observed in male but not female offspring (Magaton et al. 2007). Overall these studies investigating the consequences of maternal nutrition and metabolic status support the contention that these adverse maternal factors affect fetal development and increase the risk of hypertension and cardiovascular disease in later life.

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## Maternal Stress and Glucocorticoids

### Maternal Stress

Natural glucocorticoids (cortisol in humans and sheep or corticosterone in rodents) are released during physiological stress. In a study of women with frequent miscarriage, stress, as assessed by raised maternal cortisol levels, was associated with increased miscarriage (Nepomnaschy

et al. 2006). An association between maternal stress and impaired cognitive and motor development in the infant has been reported (Buitelaar et al. 2003). Similarly, some women exposed to stressful events such as the 9/11 terrorist attack on the World Trade Center had babies with reduced birth weight (Valladares et al. 2009) and head circumference (Engel et al. 2005). In a nationwide population-based study in Denmark, fetal exposure to stress as a result of maternal bereavement such as loss of a relative during pregnancy or the year before pregnancy (50,940 participants) was associated with higher rates of heart disease and hypertension at follow-up (up to 40 years of age) (Plana-Ripoll et al. 2016). In contrast, in a population of 957 offspring born to women characterized as experiencing psychosocial stress during pregnancy, a positive association between maternal stress and offspring BMI as well as a negative association between maternal stress and offspring systolic blood pressure at age 20 years was observed (Bhat et al. 2015). Thus, while there is evidence in humans to suggest that maternal stress may program fetal development and adult disease, the data are not strong and are often subjective.

## Glucocorticoids and Development

Glucocorticoids are essential for development of all organ systems (Kitraki et al. 1997). Clinically, synthetic glucocorticoids (betamethasone or dexamethasone) may be administered to women at risk of preterm delivery, as glucocorticoids hasten the maturation of the preterm infant lung (Liggins and Howie 1972). Additionally, synthetic glucocorticoids have been administered to pregnant women at risk of having a baby with congenital adrenal hyperplasia, which may result in cortisol levels 60-fold higher than endogenous cortisol levels (Speiser et al. 2010). Such doses are considered necessary to reduce potential genital virilization of the female fetus (Clayton and Brock 2012). Maternal glucocorticoid administration in the form of prednisone or prednisolone is also prevalent in women with autoimmune conditions and asthma (Murphy et al. 2005). Thus, while clinical use of synthetic glucocorticoids is often

beneficial to the fetus, the long-term effects on offspring are less well understood. However, one study has reported an association between antenatal exposure to synthetic glucocorticoids and increased blood pressure in adolescence (Doyle et al. 2000).

## Models of Glucocorticoid Programmed Hypertension

There is strong evidence from experimental models that fetal exposure to glucocorticoids can program adult onset disease. In the rat, administration of dexamethasone throughout pregnancy resulted in low birth weight and elevated arterial pressure in 60-day-old offspring (Celsi et al. 1998). Administration of dexamethasone on days 15–16 of gestation resulted in hypertension in both male and female offspring, but administration on days 17–18 of gestation resulted in hypertension only in male offspring at 3 months of age (Ortiz et al. 2001). Further, administration on other days had no effect (Ortiz et al. 2001). In the Ortiz et al.'s study, effects on blood pressure occurred without a reduction in birth weight (Ortiz et al. 2001). Corticosterone administration on days 14–15 of gestation in the rat (Singh et al. 2007) has been shown to result in an increase in blood pressure in male and female offspring. However, not all studies have found an association between glucocorticoids and fetal programming of hypertension. For example, administration of dexamethasone between days 15 and 21 of gestation in rats resulted in growth restriction but caused hypotension in both male and female offspring (O'Regan et al. 2008). Such differences between studies may be due to the experimental methods used, such as blood pressure measurement methods (radiotelemetry vs. tail cuff) or differences in the timing and dose of dexamethasone administration.

Administration of dexamethasone to pregnant ewes between days 26 and 28 of gestation resulted in hypertension in both male and female offspring with a greater increase in males (Dodic et al. 2002). Again, no significant effect on birth weight was observed, which suggests that the fetal

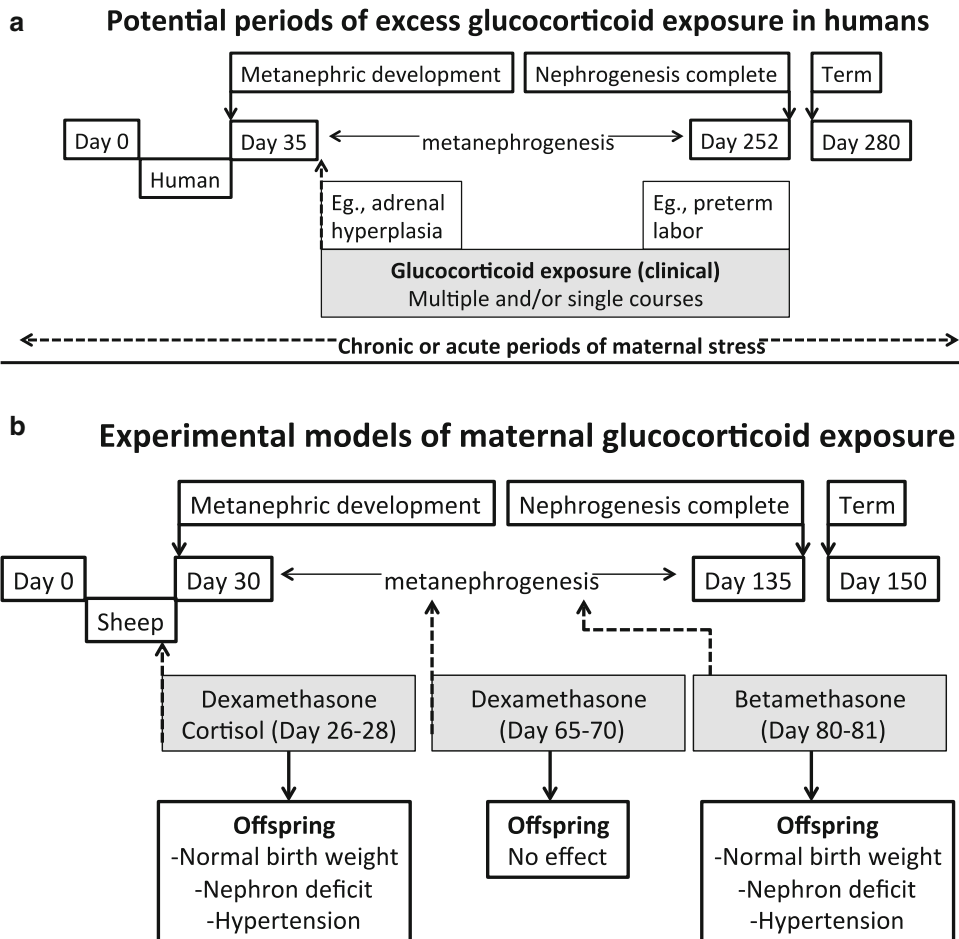


programming of hypertension can occur without notable outward signs at birth (Dodich et al. 2002). However, administration of dexamethasone between gestation days 65 and 70 had no effect on offspring blood pressure (Dodich et al. 1998). In another study, administration of betamethasone to the pregnant ewe between days 80 and 81 of gestation resulted in an increase in blood pressure in male and female offspring (Zhang et al. 2010). Since the intra-arterial measurement of blood pressure in conscious sheep is reliable, the effects of elevations in maternal glucocorticoid levels on offspring blood pressure appear to be affected by

the timing and dose of glucocorticoid administration (Fig. 2).

### Glucocorticoids and Placental Function

The placenta regulates the passage of glucocorticoids via the enzyme 11-beta-hydroxysteroid dehydrogenase type 2 (11βHSD2) by inactivating cortisol or corticosterone. Although inactivation of physiological levels of cortisol by 11βHSD2 is ~90% (Benediktsson et al. 1997), excess cortisol can reduce the efficiency of this enzyme (Mairesse



**Fig. 2** Schema depicting the relative timing of nephrogenesis in humans (a) and sheep (b). Illustrated in humans are the potential periods when the fetus might be exposed to excess glucocorticoid levels and thus be

vulnerable to programming effects. Illustrated in sheep are the periods when glucocorticoids have been administered experimentally and the outcomes of those studies

et al. 2007). Moreover, the activity of  $11\beta$ HSD2 appears to be dependent on the sex of the fetus with placentas from female fetuses having greater  $11\beta$ HSD2 activity than placentas from male fetuses (Stark et al. 2009). Sex-specific differences between the placental response to glucocorticoid in terms of glucose and nutrient transport, expression of  $11\beta$ HSD2, and the glucocorticoid receptors have also been reported in mice (Cuffe et al. 2011). Similar sex-specific effects on placental structure and function have also been observed following prenatal hypoxia in the mouse (Cuffe et al. 2014) and following maternal dietary protein restriction in the pig (Shang et al. 2016), indicating that excess transport of glucocorticoids may be important in various models of maternal compromise.

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## Other Maternal Influences and Offspring Blood Pressure

Many other maternal factors with the potential to influence fetal development have been examined for their potential to prime the offspring to develop hypertension in later life. Maternal smoking or exposure to smoke has been associated with an increase in blood pressure in humans (Blake et al. 2000; Geerts et al. 2007; Han et al. 2015; Oken et al. 2005). However, lack of an association with smoke exposure has also been reported (Leary et al. 2013). Experimentally, prenatal nicotine administration to the pregnant rat results in higher blood pressure in offspring (Block et al. 2015), but the effect is strain dependent (Toledo-Rodriguez et al. 2012). Maternal alcohol consumption during pregnancy is well known to be associated with a range of adverse fetal and developmental outcomes in the offspring depending on the amount of consumption (Kenna et al. 2012). Administration of alcohol to pregnant rats for just 2 days of gestation (13.5–14.5) results in blood pressure elevations in both male and female offspring (Gray et al. 2010). Sleep deprivation has been associated with abnormalities in autonomic function (higher day and night-time heart rate) among non-pregnant adults who sleep 5 hours per day (Grimaldi et al. 2016), and less

sleep has been associated with increased arterial pressure (Cappuccio et al. 2007). However, the effects of sleep deprivation during pregnancy in humans have not been studied in detail. In the rat, restricting sleep to only 4 hours per day either between days 14 and 20 of pregnancy (Thomal et al. 2010) or between days 0 and 20 (Lima et al. 2014) was associated with increased blood pressure in adult offspring.

The maternal environment has a profound impact on fetal development. While low birth weight is a surrogate marker in humans of the impact of an adverse maternal environment, in animal studies it is clear that fetal development can be adversely affected without a change in birth weight. How the maternal environment influences health outcomes of the offspring is currently incompletely understood.

## Epigenetics

There is evidence that developmental programming includes epigenetic responses to the perinatal environment. Epigenetic mechanisms regulate genomic function and gene expression without altering the primary DNA sequence, and these changes can be transmitted across generations. The primary epigenetic mechanisms involve DNA methylation, histone modification, and microRNAs. DNA methylation has been the most studied epigenetic mechanism, and alterations in DNA methylation have been reported in some developmental programming models of hypertension. For example, hypomethylation of insulin-growth factor type II (IGF2, maternally imprinted) has been observed in adults whose mothers were exposed to the Dutch winter famine during the periconception period when compared to their nonexposed siblings (Heijmans et al. 2008). Additionally, hypomethylation of IGF2 was not observed in adults whose mothers were only exposed to famine during late gestation (Heijmans et al. 2008). A follow-up study in the Dutch Famine cohort demonstrated hypermethylation of genes involved in cardiovascular function, metabolism, and inflammation, and again the methylation status was dependent on

timing of exposure to the famine and fetal sex (Tobi et al. 2009).

DNA methylation is mediated by enzymes involved in one-carbon metabolism pathways. The activity of these enzymes is dependent on levels of various micronutrients including choline, folate, vitamins B6 and B12, methionine, and retinoic acid. In sheep, a maternal methyl-deficient diet (restricted in folate, vitamin B12 and methionine) from 8 weeks prior to conception until 6 weeks after conception resulted in increased DNA methylation and elevated blood pressure in male offspring studied at 23 months of age (Sinclair et al. 2007). Moreover, alterations in methylation of key pathways involved in blood pressure regulation have been reported. Hypomethylation of promoter regions of ACE-1 and increased expression of microRNAs regulating translation of ACE-1 mRNA were observed in brains of mouse fetuses from dams fed a low-protein diet in the second half of gestation (Goyal et al. 2010). A maternal low protein diet in the rat was reported to result in increased expression of the angiotensin type 1b receptor associated with the undermethylation of the proximal promoter region in the adrenal gland in 1-week-old offspring (Bogdarina et al. 2007). The same group demonstrated that treatment of the dams with metyrapone (inhibitor of 11 $\beta$ HSD2) between days 0 and 14 of gestation appeared to reverse the observed methylation changes and was associated with a reversal of hypertension previously observed in these offspring, suggesting alterations in methylation early in pregnancy in this model may be influenced by maternal glucocorticoids (Bogdarina et al. 2010).

## Transgenerational Programming

Epigenetic mechanisms may also be responsible for transgenerational programming, as DNA methylation patterns have been demonstrated to persist from one generation to another (Jones and Liang 2009). Hypertension and vascular dysfunction induced in the F1 generation following dietary protein restriction during pregnancy in rats

has been reported as transmitted to the F3 generation in the presence of normal nutrition in the F2 generation (Torrens et al. 2008). Gestational protein restriction in the F0 generation of rat dams has been associated with altered promoter methylation in the F2 generation, even when the F1 generation was not nutrient restricted (Burdge et al. 2007). Similarly, adequately nourished F3 generation offspring (grand-offspring) of dams malnourished during gestation and the perinatal period (F0 generation) have been reported to have alterations in glucose metabolism (Benyshek et al. 2006).

Associational studies indicate that the paternal environment may also play a role in programming, at least in terms of metabolic and cardiovascular disease. It has been demonstrated that caloric restriction in men just before puberty was associated with a longer lifespan among their grandchildren as compared to children whose grandfathers were overnourished (Bygren et al. 2001). Moreover, excess calorie intake of the paternal grandfather was associated with a four-fold increase in the risk of mortality from diabetes in the grandchildren, but undernutrition of the father and paternal grandmother was associated with less cardiovascular disease in sons (Kaati et al. 2002).

Blood pressure is regulated by multiple organ systems, including the kidney, heart, vasculature, and the nervous system. All these systems are affected by perturbations to the maternal environment. Below we summarize the key factors that may contribute to developmental programming of hypertension.

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## Fetal Adaptations and the Programming of Hypertension

In response to a suboptimal environment, the fetus undergoes adaptations that promote chances of survival but increase the risk of disease with aging. In terms of the programming of hypertension, the evidence indicates an important role for structural and functional adaptations in the kidneys. Hence, the kidney is a major focus of the

following discussion, but other components of the cardiovascular and nervous systems are also considered.

## The Kidney

The kidneys play a dominant role in blood pressure homeostasis. A common finding in many models of fetal programming has been the presence of small kidneys at birth. The evidence in humans is not as extensive, but it supports the hypothesis that altered kidney development is associated with adult hypertension (Luyckx et al. 2013). The link between hypertension and nephron number was initially documented in models of hypertension in the rat, 5/6th nephrectomy, and later in diabetic rats, in which compensatory glomerular hyperfiltration driven in part by an increase in glomerular capillary hydraulic pressure resulted in glomerulosclerosis and further nephron loss exacerbating the hypertension (Brenner et al. 1988, 1996). The resulting nephron deficit increases single glomerular flow, and thus single glomerular pressure, causing hyperfiltration and eventually glomerular hypertrophy and glomerulosclerosis. This evidence suggested that alterations in glomerular and tubular function and structure and/or alterations in mechanisms regulating sodium transport may be key features in mediating hypertension. Indeed, alterations in nearly all components of the kidney have been observed in numerous models of developmental programming of hypertension. Reported renal phenotypes include a reduction in nephron number and alterations in renal function, sodium transport, the renin-angiotensin-aldosterone system (RAAS), and renal sympathetic nerves that regulate kidney function.

## Nephron Number

In normal adult human kidneys, total nephron number varies more than 10-fold, and nephron number is directly correlated with birth weight (Hughson et al. 2003) (Luyckx et al. 2013) – the lower the birth-weight, the lower the nephron number. Nephrogenesis in the human is complete

prior to term birth (Hinchliffe et al. 1991); thus, any deficit in nephron number at birth (nephron endowment) is permanent. It is also known that nephron number decreases with age (Bertram and Hoy 2016; Denic et al. 2016). Maternal factors that limit nephron endowment coupled with age-related nephron loss have been linked to the programming of hypertension in adulthood (Luyckx et al. 2013).

Only a handful of studies have investigated the association between human nephron number and hypertension. In a small German study of young Caucasian adults who had died accidentally, Keller et al. (2003) found that the kidneys of persons with no history of hypertension (1,402,360 nephrons) contained twice as many nephrons as age-matched persons with a history of hypertension (7,02,379 nephrons). Lower nephron numbers have also been reported in hypertensive Caucasian Americans (7,54,319) compared with normotensive Caucasian Americans (9,23,377) (Hoy et al. 2006; Hughson et al. 2006, 2008). Hoy et al. (2006) reported that the kidneys of hypertensive Australian Aborigines contained approximately 2,50,000 fewer nephrons than kidneys of nonhypertensive Aborigines. However, nephron number appears to be similar in normotensive and hypertensive African Americans (Hughson et al. 2006, 2008).

In experimental studies, low nephron endowment in offspring has been consistently observed following maternal dietary protein restriction, whether the protein intake was reduced for all of gestation (Woods et al. 2004), only late in gestation (Vehaskari et al. 2001; Woods et al. 2004), from prior to mating until lactation (Zimanyi et al. 2004), or lifelong (Hoppe et al. 2007), but not when protein restriction occurred only in the first half of gestation (Woods et al. 2004). Cross-fostering of offspring from low-protein dams (late gestation) onto normal protein dams from birth until weaning prevented this nephron deficit (Siddique et al. 2014). Additionally, in the uteroplacental insufficiency model of programmed hypertension and nephron deficiency, cross-fostering of pups onto control dams prevented the nephron deficit and hypertension

(Wlodek et al. 2007). Low nephron endowment in offspring has also been documented following maternal glucocorticoid administration (Celsi et al. 1998; Dickinson et al. 2007; Moritz et al. 2011; O'Sullivan et al. 2013; Ortiz et al. 2001; Singh et al. 2007; Wintour et al. 2003; Zhang et al. 2010), maternal diabetes (Hokke et al. 2013; Tran et al. 2008), and maternal alcohol exposure (Gray et al. 2010). However, it should be noted that the reduction in nephron number observed in these models has not always been associated with hypertension in the offspring (Dickinson et al. 2007; Hoppe et al. 2007; Zimanyi et al. 2004). A caveat to many of these studies is that nephron number was determined in adult kidneys; thus, a distinction between low nephron endowment at birth and nephron loss with age cannot be made. However, the many studies that document nephron number in juvenile animals are less likely to be influenced by this issue. Finally, a decrease in nephron number in the fetal kidney has been reported following prenatal hypoxia (Wilkinson et al. 2015). Thus, prenatal insults have immediate effects on kidney development. Therefore, it is accepted that a low nephron number at birth is a common response to a perinatal insult.

### Glomerular Function

In models of programmed hypertension associated with decreased nephron number, glomerular filtration rate (GFR) has been shown to be either reduced, unchanged, or increased. GFR has been shown to be reduced following maternal calorie restriction (Almeida and Mandarim-de-Lacerda 2005), dietary protein restriction (Vehaskari et al. 2001; Woods et al. 2001), maternal glucocorticoid administration (Celsi et al. 1998; Woods and Weeks 2005; Xue et al. 2015; Zhang et al. 2010), maternal alcohol administration (Gray et al. 2010), and maternal diabetes (Franca-Silva et al. 2016; Magaton et al. 2007; Tran et al. 2008). A reduction in renal functional reserve in response to amino acid infusion has also been observed in offspring of diabetic rats (Abi Khalil et al. 2010). Other studies have reported no changes in GFR following these same perturbations (Jackson et al. 2012; Moritz et al. 2011; Ortiz et al. 2003; Wintour et al. 2003). However, this has been

interpreted as evidence of glomerular hyperfiltration (Lima et al. 2014; Thomal et al. 2010). In addition to changes in GFR, increases in urinary albumin excretion or proteinuria and glomerulosclerosis have been demonstrated in many of these models (Celsi et al. 1998; Jackson et al. 2012; Ortiz et al. 2003; Tran et al. 2008; Yamada-Obara et al. 2016). Together such evidence suggests that the kidney with fewer nephrons undergoes adaptations to limit the loss of function, but this is associated with renal injury (albuminuria) that will progress with time, resulting in a vicious cycle of further nephron injury and loss of function ultimately leading to hypertension (Brenner et al. 1988, 1996; Luyckx et al. 2013).

### Tubular Function

Tubulointerstitial injury may alter renal tubular function, in turn, affecting sodium homeostasis. Tubulointerstitial fibrosis is observed in models of programmed hypertension (Glastras et al. 2016, 2015; Yamada-Obara et al. 2016), together with alterations in pathways regulating fibrosis, inflammation, and oxidative stress (Chen et al. 2010; Franca-Silva et al. 2016; Glastras et al. 2015; Tran et al. 2008; Yamada-Obara et al. 2016). Additionally, changes in gene and/or protein expression of sodium, calcium, and water channels have been documented in several models of programmed hypertension (Alwasel and Ashton 2009; Dagan et al. 2007; Manning et al. 2002; Moritz et al. 2011).

### The Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system (RAAS) is a powerful modulator of arterial pressure and renal function in adults (Digne-Malcolm et al. 2016) and is essential for normal renal development (Song et al. 2011). Alterations in nearly all components of the RAAS have been observed in models of programmed hypertension. Reduced intrarenal renin has been observed following a maternal high-fat diet (lard enriched) in rat offspring (Armitage et al. 2005), maternal dietary protein restriction in neonatal rats (Woods et al. 2001), and placental insufficiency in fetal

sheep (Zhang et al. 2000). Decreased expression of both the angiotensin II type 1 receptor (AT<sub>1</sub>R) and the type 2 receptor (AT<sub>2</sub>R) was observed following protein restriction throughout pregnancy (Mesquita et al. 2010). In contrast, maternal diabetes has been reported to result in increased expression of angiotensinogen, angiotensin-converting enzyme (ACE), AT<sub>1</sub>R (Chen et al. 2010), and renin (Tran et al. 2008) in 2-month-old offspring. Maternal protein restriction has been shown to significantly increase plasma ACE-1 (Langley-Evans and Jackson 1995) and renal AT<sub>1</sub>R expression in offspring (Manning and Vehaskari 2001). Forty-eight hours of glucocorticoid treatment early in gestation increased expression of the AT<sub>1</sub>R and AT<sub>2</sub>R in the kidneys of sheep (Moritz et al. 2002) and rat (Singh et al. 2007) offspring. In addition to alterations in the expression of the RAAS, changes in pressor, central, and renal hemodynamic responses to angiotensin II have been reported. In sheep, maternal food restriction resulted in enhanced pressor responses to angiotensin II infusion in the fetus (Edwards and McMillen 2001), maternal dexamethasone administration increased pressor responses to central (intracerebroventricular) administration of angiotensin II in adult offspring (Dodic et al. 2006), and maternal betamethasone has been shown to alter renal hemodynamic and tubular sodium excretion to Ang (1–7) in 6-month male and female offspring (Tang et al. 2010). Moreover, ACE-inhibition in the dietary protein restriction (Langley-Evans and Jackson 1995; Manning and Vehaskari 2001) and placental insufficiency (Grigore et al. 2007) models of programmed hypertension has been demonstrated to normalize blood pressure in offspring. These differences in findings likely reflect the severity of the insult and the age at which observations were made. It has been suggested that alterations in the RAAS in models of fetal programming also reflect changes in the RAAS with age (Kett and Denton 2011).

Distinct sex-differences in the programming of arterial pressure have been reported, with females protected during the reproductive years (Moritz et al. 2010; Ojeda et al. 2014). Many of the sex-differences observed in models of

programming may in part be attributable to alterations in the RAAS. In the reduced uterine perfusion model of placental insufficiency, pretreatment with enalapril normalized blood pressure in male offspring, but pressor responses to angiotensin II were still enhanced on this background of ACE inhibition (Ojeda et al. 2010). Moreover, this enhanced pressor response was blunted following castration of the offspring implicating a role for testosterone in this model (Ojeda et al. 2010). In this same model, female offspring from mothers that experienced placental insufficiency were normotensive but had enhanced pressor responses to angiotensin II which was augmented following ovariectomy (Ojeda et al. 2011). In this placental insufficiency model of programmed hypertension, early reproduction senescence has been observed in female offspring along with an increase in blood pressure by 12 months of age. This increase in blood pressure with age was prevented by androgen receptor blockade in females, but the response was modulated by ACE inhibition in the growth-restricted female offspring (Dasinger et al. 2016b). Conversely, in growth-restricted male offspring, the increase in blood pressure with age was not modulated by ACE inhibition (Dasinger et al. 2016a). In male rat offspring of protein-restricted dams, the expression of renal renin and angiotensin II was reduced during development (Woods et al. 2001), but not in females (Woods et al. 2005). Thus, these studies suggest that sex differences in programmed adult blood pressure may result from sex-specific programming of the RAAS during nephrogenesis (Moritz et al. 2010).

### Renal Sympathetic Nerves

Renal nerves play an important role in the regulation of glomerular and tubular function, and evidence demonstrates that neural control of renal function is altered by perinatal insults. In models of maternal overnutrition programmed hypertension, an increase in renal noradrenaline content (an index of sympathetic innervation density) was observed in mouse offspring (Samuelsson et al. 2016), and increased renal sympathetic nerve activity was observed in rabbit offspring (Prior et al. 2014). An increase in renal noradrenaline

content was also reported in kidneys of hypertensive female rabbit offspring born to hypertensive mothers (Maduwegedera et al. 2007). Moreover, in the utero-placental insufficiency model of programmed hypertension, bilateral renal denervation normalized blood pressure (Alexander et al. 2005) and prevented the age-related increase in blood pressure in growth-restricted offspring (Intapad et al. 2013). Bilateral renal denervation of rat offspring whose mothers were treated with dexamethasone between days 14 and 18 of gestation resulted in normalization of blood pressure to levels similar to that of control animals (Dagan et al. 2008). Additionally, in this model, the increased expression of proximal tubule  $\text{N}^+/\text{H}^+$  exchanger (Dagan et al. 2007) and activities of the thick ascending limb NKCC2 and distal convoluted tubule NCC (Dagan et al. 2009) were normalized following renal denervation (Dagan et al. 2008). Taken together, these findings suggest that programmed hypertension is associated with alterations in the neural control of renal function which contribute to the dysregulation of blood pressure homeostasis.

### **Programming of Blood Pressure: Involvement of Other Organ Systems**

Altered renal development has been strongly implicated in the pathogenesis of programmed adult hypertension, yet it is likely that other organ systems are also involved. Indeed, disturbances to cardiac and vascular structure and function can significantly contribute to hypertension and alterations in these systems are present in models of programmed hypertension.

### **Cardiac Structure and Function**

Left-ventricular hypertrophy is linked to heart disease, including that associated with low birth weight (Vijayakumar et al. 1995). It has been suggested that a reduction in the number of terminally differentiated cardiomyocytes at birth results in hypertrophy of those cardiomyocytes present in order to maintain cardiac function at a level appropriate for body size, with detrimental consequences in the long term. In a recent nationwide

study in Denmark, pregestational diabetes was associated with significantly greater prevalence of congenital heart disease in offspring, regardless of time of diabetes onset, duration of diabetes, and diabetes type (Type 1 vs. Type 2) (Oyen et al. 2016). The cardiac phenotype in models of fetal programming that are associated with low birth weight has been extensively studied and reviewed (Wang et al. 2012; Zohdi et al. 2014). A reduction in cardiomyocyte number and/or increase in cardiac hypertrophy have been observed in offspring following maternal protein restriction (Corstius et al. 2005) and vitamin D deficiency (Gezmish et al. 2009) in the rat and restriction of placental function in the sheep (Morrison et al. 2007). In mice maintained on a high-fat diet from weaning, an increase in heart weight and alterations in cardiac gene expression have been reported with male and female offspring having reduced expression of cyclin G1 in the left ventricles but increases in brain natriuretic peptide (BNP) in females and reduced in males compared with offspring maintained on a normal diet (Elahi and Matata 2014). A high-fat diet only during gestation in the rat resulted in cardiac hypertrophy in male offspring but diastolic and systolic dysfunction in both male and female offspring aged 3 months (Xue et al. 2015). Increased gene and protein expression of  $\text{AT}_2\text{R}$  together with increased susceptibility to ischemia reperfusion injury was observed in male but not in female offspring of high-fat fed mothers (Xue et al. 2015). In a sheep model of placental insufficiency, a role for insulin-like growth factors has been implicated in the early life pathogenesis of cardiac hypertrophy (Wang et al. 2012).

### **Vascular Structure and Function**

Vascular dysfunction has been observed in persons who had low birth weight with evidence of impairment of both endothelium-dependent and independent vasodilation with less evidence of impairment in vasoconstriction (Goh et al. 2001). In low birth weight infants, endothelium-dependent vasodilation was reduced in response to acetylcholine (Leeson et al. 2001; Martin et al. 2000, 2001) and a lower flow-mediated dilation was observed in nonobese children born small for gestational age

compared with obese children born appropriate for gestational age (Jouret et al. 2011).

Impaired vascular responses have also been observed in models of programmed hypertension (Khan et al. 2005; Taylor et al. 2004). In swine, a high-energy diet fed prior to pregnancy and throughout pregnancy and lactation reduced both endothelium-dependent (bradykinin) and independent (sodium nitroprusside) mediated vasorelaxation in femoral arteries of male and female offspring aged 3 months, with no improvements in outcomes observed when offspring from high energy diet dams were placed on a normal diet postweaning (Taheripour et al. 2014). In Japanese macaques, a maternal high-fat diet from up to 5 years prior to pregnancy through to lactation resulted in a significant reduction in acetylcholine-dependent relaxation in the abdominal aorta, increased intimal thickness, and increased expression of markers of vascular inflammation including vascular endothelial growth factor, tumor necrosis factor alpha, and intracellular adhesion molecule in juvenile (13 month old) female offspring (Fan et al. 2013). Switching these offspring to a normal diet at weaning partially improved these phenotypes (Fan et al. 2013). In the mouse, in hypertensive male offspring of high-fat dams, reduction in endothelium-dependent vasodilation has been observed at 15 weeks of age with exacerbation of the phenotype by 30 weeks of age and this was associated with reduced nitric oxide production (Torrens et al. 2012).

A role for nitric oxide has also been reported in hypertension in rats programmed by maternal diabetes. Induction of diabetes late in gestation (day 13) resulted in a blunting of angiotensin II-mediated contractility in aortas of both male and female offspring, following nitric oxide synthase inhibition and Cu/Zn superoxide dismutase inhibition (Katkhuda et al. 2012). Additionally, nicotinamide adenine dinucleotide phosphate-stimulated production of superoxide was significantly reduced but only in male offspring (Katkhuda et al. 2012). In earlier studies by this group, late gestation diabetes enhanced aortic contractility to endothelin-1 and noradrenaline and reduced acetylcholine-dependent relaxation in female offspring, whereas in male offspring

responses to vasoconstrictors did not differ to controls but relaxation to both sodium nitroprusside and acetylcholine was increased (Segar et al. 2009). In male offspring of diabetic rats, decreased aortic vasodilation in response to an analog of prostacyclin (PGI<sub>2</sub>), together with decreased expression of the prostacyclin receptor in the aorta, was observed at 3 months of age, prior to onset of hypertension (Duong Van Huyen et al. 2010). Together these studies suggest that vascular dysfunction can be both a result of hypertension and, possibly, a precursor to hypertension of developmental origin.

### Autonomic Nervous System

There is strong evidence that overactivity of the sympathetic nervous system contributes to the pathogenesis of essential hypertension (Grassi et al. 2015). There is also evidence of altered sympathetic nerve activity in models of programmed adult hypertension from both human and animal studies. In 58-year-old men and women who were born during the time of the Dutch famine (1944–1945), an increase in blood pressure in response to a stress test was observed in individuals whose mothers were exposed to the famine early in gestation (Painter et al. 2006). A positive, independent association between birth weight and baroreflex sensitivity was observed in healthy 22- to 24-year-old women (Leotta et al. 2007). In animal studies, hypertension in offspring resulting from maternal high fat intake was associated with enhanced pressor responses to restraint stress in the rat (Samuelsson et al. 2010). Additionally, in these animals, the hypertension was abolished by alpha-1 and beta-adrenergic blockade but enhanced pressor responses to leptin challenge remained intact, suggesting that the hypertension may originate from sympathoexcitatory hyper-responsiveness from early in development (Samuelsson et al. 2010). In rabbits, a maternal high-fat diet results in elevated heart rate and renal sympathetic nerve activity and enhanced renal sympathetic responses to air jet stress (Prior et al. 2014). Additionally, both pressor responses and renal sympathetic nerve activity were enhanced in response to intracerebroventricular leptin (Prior et al. 2014). This indicates sympathetic overactivity may be a



common underlying mechanism in maternal obesity-induced hypertension. Enhanced sympathetic and hypothalamic-pituitary responses have been reported in offspring of sheep following prenatal betamethasone exposure (Shaltout et al. 2011). Enhanced pressor responses to restraint stress have also been observed in offspring of mice following prenatal dexamethasone administration (O'Sullivan et al. 2013).

Taken together, the current evidence suggests that numerous and diverse mechanisms promote the development of hypertension programmed by an adverse perinatal environment. Determining what mechanisms are primary initiating factors of the hypertension and which are secondary adaptations to the hypertension will aid in devising therapeutic interventions to prevent programmed hypertension.

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### **Interventions to Ameliorate a Challenging Start to Life**

Clinical strategies to prevent or reverse the effects of developmental programming are gaining momentum. Avenues currently under investigation involve micronutrient supplementation and strategies targeting oxidative stress and nitric oxide bioavailability. In the calorie restriction model, supplementing pregnant rats on hypocaloric intake (50% reduction) with micronutrients (selenium, vitamin C and E, and folate) prevented hypertension and endothelial dysfunction in offspring (Franco Mdo et al. 2009). Supplementation with individual micronutrients may be just as beneficial. In the dietary protein restriction model of hypertension in the rat, supplementing the pregnant dams with folate (Torrens et al. 2006) and choline (Bai et al. 2012), both of which are involved in DNA methylation, normalized blood pressure in the offspring. Supplementing the postweaning diet of the offspring of protein-restricted dams with taurine, an amino acid with anti-inflammatory and antioxidant properties, partially improved blood pressure and vascular function and reduced production of reactive oxygen species in the male offspring (Maia et al. 2014). Increasing nitric

oxide bioavailability through maternal citrulline supplementation reduced the effects of maternal low protein diet on birth weight (Bourdon et al. 2016); in another study L-citrulline supplementation improved blood pressure outcomes in offspring following maternal dexamethasone treatment (Tain et al. 2015) and in offspring of spontaneously hypertensive rats (Tain et al. 2015). Interestingly, in the maternal calorie restriction model, supplementation of the maternal diet with L-citrulline throughout pregnancy and lactation improved renal function and rescued nephron number in offspring, but hypertension was still present in offspring (Tain et al. 2010).

The onset of renal dysfunction and hypertension were delayed by treatment with either the substrate for nitric oxide synthase (L-arginine) or the superoxide scavenger, tempol, in a rat model of postnatal reduction of renal mass (Carlstrom et al. 2013). Similar outcomes were observed in models of dietary protein restriction and maternal glucocorticoid administration (Rexhaj et al. 2011; Roghair et al. 2011). Attenuation of oxidative stress was achieved by dietary supplementation with n-3 long-chain polyunsaturated fatty acids (fish oils) in programmed models of hypertension (Makrakis et al. 2007; Wyrwoll et al. 2006), and partial improvements in vascular function were observed following maternal dietary supplementation with omega 6 (conjugated linoleic acid) fatty acid in the model of maternal overnutrition (high fat intake) (Gray et al. 2015). In another study, 50% food restriction throughout gestation in the rat resulted in increased systolic blood pressure in 150-day-old male offspring, and this increase in blood pressure was prevented in offspring treated with growth hormone between postnatal days 3 and 21 (Gray et al. 2013). Addition of pravastatin to the drinking water of dams on a high-fat diet from mid-gestation to lactation normalized heart weight and blood pressure in female offspring to levels seen in offspring of animals that had been on a normal diet and also normalized expression of cyclin G1 in male and female offspring (Elahi and Matata 2014).

Although such findings from experimental settings are promising, many questions remain regarding the timing and dose of interventions. In humans,

gestational weight gain and birth weight are strongly correlated with micronutrient intake, yet clinical trials examining micronutrient supplementation during pregnancy have not demonstrated long-term health benefits for offspring (Devakumar et al. 2016). However, the timing of such interventions may be critical in situations of developmental programming, and it may be more important to examine preventive interventions, as opposed to treatment measures, in such circumstances.

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## Concluding Remarks

The perinatal environment can profoundly influence the developing fetus. A suboptimal maternal environment can adversely affect organogenesis (kidney, heart, vasculature, and nervous system), leading to hypertension and cardiovascular disease in adulthood. Strategies to optimize maternal health and early childhood nutrition would likely reduce the global burden of hypertension and cardiovascular disease.

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## Cross-References

- ▶ [Endothelial Dysfunction and Vascular Remodeling in Hypertension](#)
- ▶ [Hypertensive Models and Their Relevance to Pediatric Hypertension](#)
- ▶ [Insulin Resistance and Other Mechanisms of Obesity Hypertension](#)
- ▶ [Ions and Fluid Dynamics in Hypertension](#)
- ▶ [Neurohumoral and Autonomic Regulation of Blood Pressure](#)

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## Abstract

A number of family studies in the 1960s and 1970s showed that a familial tendency to high (or low) blood pressure is established early in life. However, it remained unclear whether shared genes or shared environment caused the blood pressure aggregation within families. Classically, special study designs such as adoption or twin studies are necessary to effectively discriminate genetic from shared environmental influences. Furthermore, estimates of the relative influence of genetic and environmental factors derived from cross-sectional studies do not provide information on underlying genetic and environmental sources of continuity and change in the development of (high) blood pressure from childhood onward. The aim of the current chapter, therefore, is to review the available literature of genetically informative epidemiologic studies to address two issues:

the potential causes of familial aggregation of blood pressure and the age dependency of genetic or environmental sources of blood pressure variation (and covariation) within and between families.

## Keywords

Heritability • Family environment • Family study • Twin study • Age dependency

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## Introduction

In the first half of the last century, evidence for the familial aggregation of (elevated) blood pressure (BP) levels was largely anecdotal and based on case reports of clinicians until a number of large family studies in the 1960s showed familial resemblance of BP with correlations around 0.20 among first-degree relatives (Johnson et al. 1965; Miall et al. 1967). Relatively few observations were made in children in these early studies, which initiated a number of research projects in the 1970s investigating whether familial aggregation of BP could be detected in childhood. Zinner et al. (1971), for example, measured BP in 721 children between 2 and 14 years of age from 190 families. Sib-sib and mother-child correlations of 0.34 and 0.16 for systolic BP (SBP) and 0.32 and 0.17 for diastolic BP (DBP) were found. These results were largely confirmed in a follow-up of the same cohort 4 years later (Zinner et al. 1974). Findings were extended to even younger ages by two further studies that showed significant sibling BP aggregation with 1-month-old infants (Hennekens et al. 1976) and significant parent-offspring correlations between mothers and their newborn infants (Lee et al. 1976).

Thus, these studies showed that a familial tendency to high (or low) BP is established early in life, but a number of questions remained unanswered. For example, it was unclear whether shared genes or shared environment caused the BP aggregation within families. Unique study designs such as adoption or twin studies are necessary to effectively discriminate genetic from shared environmental influences, because these sources of familial resemblance are confounded within nuclear families. Furthermore, estimates of the relative influence of genetic and environmental factors derived from, for example, cross-sectional twin studies are merely “snapshots” of a specific point in time: they do not give information on underlying genetic and environmental sources of continuity and change in the development of cardiovascular disease or their intermediate traits such as BP or lipids (Snieder et al. 1999, 1995). Genetic (or environmental) influences on BP may thus be age dependent in two different

manners (Snieder 2000). Firstly, the magnitude of these influences on BP can differ with age. Secondly, different genes or environmental factors may affect BP at different ages. For example, BP genes may switch on or off during certain periods in life, i.e., age-dependent gene expression.

Therefore, in this chapter we will review the available literature on twin and family studies to address two issues: the potential causes of familial aggregation of BP and the age dependency of genetic or environmental sources of BP variation (and covariation) within and between families.

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## Causes of Familial Aggregation of BP

### Rationale Behind Classic Twin Studies

Two approaches that frequently have been used to study the contributions of genes and environment to variation in BP levels are family and twin studies. The first approach studies the resemblance in BP between parents and offspring or between siblings in nuclear families. The second approach examines the similarity of BP in monozygotic (MZ) and dizygotic (DZ) twin pairs.

Resemblance between family members (including twins) can arise from a common environment shared by family members and from a (partially) shared genotype. These sources of familial resemblance are confounded within nuclear families, because there is no differential sharing of genotype among first-degree relatives. Both parent-offspring and sibling pairs share on average 50% of their segregating genetic material. Therefore, special study designs are necessary to discriminate genetic from shared environmental influences. One possibility is the adoption design (Biron et al. 1976), the applicability of which is limited by practical considerations. Far more popular are twin studies, which examine phenotypic (e.g., BP) similarity of MZ and DZ twin pairs. They offer a unique opportunity to distinguish between the influences of environment and heredity on resemblance between family members. In a twin design, the separation of genetic and environmental variance is possible because MZ twins share 100% of their genetic makeup, whereas DZ

twins only share on average 50% of their segregating genes. If a trait is influenced by genetic factors, MZ twins should resemble each other to a greater extent than DZ twins.

In the classic twin method, the difference between intraclass correlations for MZ twins and those for DZ twins is doubled to estimate heritability [ $h^2 = 2(r_{MZ} - r_{DZ})$ ], which can be defined as the proportion of total phenotypic variance explained by genetic factors. Whenever the DZ correlation is larger than half the MZ correlation, this may indicate that part of the resemblance between twins is caused by shared environmental factors (Plomin et al. 1990). The twin method assumes that both types of twins share their environment to the same extent: the equal environment assumption. Although there has been some criticism of the equal environment assumption (e.g., Phillips (1993)), most studies specifically conducted to test it have proven it valid. Even if shared environment differentially affects MZ and DZ twins, it is unlikely that this has a substantial effect on the trait under study (Kendler et al. 1993; Kyvik 2000; Plomin et al. 1990). Furthermore, BP levels in twins are representative of those in the general population (Andrew et al. 2001; De Geus et al. 2001).

The use of quantitative genetic modeling to estimate these genetic and environmental variance components is now standard in twin research, and details of model fitting to twin data have been described elsewhere (Evans et al. 2003; Neale and Cardon 1992; Spector et al. 2000). In short, the technique is based on the comparison of the variance-covariance matrices (or correlations) in MZ and DZ twin pairs and allows separation of the observed phenotypic variance, which can be decomposed into several contributing factors. Additive genetic variance (A) is the variance that results from the additive effects of alleles at each contributing locus. Dominance genetic variance (D) is the variance that results from the nonadditive effects of two alleles at the same locus summed over all loci that contribute to the variance of the trait. Shared (common) environmental variance (C) is the variance that results from environmental events shared by both members of a twin pair (e.g., rearing, school, neighborhood, diet). Specific

(unique) environmental variance (E) is the variance that results from environmental effects that are not shared by members of a twin pair and also includes measurement error. Dividing each of these components by the total variance yields the different standardized components of variance, for example, the heritability which (in the absence of D) is the ratio of additive genetic variance to total phenotypic variance ( $A/A + C + E$ ).

## Heritability or Family Environment

Over the last 30 years, a large number of twin studies have been conducted investigating the relative influence of genetic and environmental factors on BP variation. Tables 1 and 2 summarize pediatric and adult studies, respectively. Only twin studies with a reasonably large sample size (>50 twin pairs total) were included. Although different methods were used to estimate heritability, it is immediately obvious from these tables that the evidence for a sizeable contribution of genetic factors to BP is overwhelming, with most heritability estimates around 50–60%. This was confirmed by a meta-analysis (Wang et al. 2015) on a total of 10,613 independent twins from 17 studies in which the weighted mean values for heritability estimates of SBP and DBP were 0.54 (95% CI, 0.48–0.60) and 0.49 (95% CI, 0.42–0.56), respectively.

The majority of these studies found no evidence for influence of shared family environment on BP. This was confirmed by the study of Evans et al. (2003) in which heritabilities of BP were estimated in more than 4000 twin pairs from six different countries. Heritabilities of DBP were between 44 and 66% across samples. For SBP, the range of estimates was even narrower at between 52 and 66%. Shared environmental factors did not play an important role, except possibly in Finland. Given the huge number of twin pairs used in these analyses, we may confidently assert that around 50% of the variance in BP is due to genetic factors. For adult twins no longer living in the same family household, this result might have been expected. However, for children it is

**Table 1** Pediatric twin studies estimating heritability ( $h^2$ ) in systolic blood pressure (SBP) and diastolic blood pressure (DBP), in ascending order according to age

Study	Pairs of twins	Age		Race	Sex	$h^2$	
		Mean (SD)	Range			SBP	DBP
Yu et al. (1990) <sup>a</sup>	274 MZ, 65 DZ	? ( ? )	0.0–1.0	Chinese	M&F	0.29–0.55	0.27–0.45
Levine et al. (1982) <sup>b</sup>	67 MZ, 99 DZ	? ( ? )	0.5–1.0	B&W	M&F	0.66	0.48
Havlik et al. (1978)	72 MZ, 40 DZ	7.0 ( ? )	?	Black	M&F	0.46	0.51
	43 MZ, 42 DZ			White	M&F	0.11	0.71
	115 MZ, 82 DZ			All	M&F	0.23	0.53
Wang et al. (1990)	75 MZ, 35 DZ	? ( ? )	7.0–12.0	Chinese	M&F	0.32	0.46
Schieken et al. (1989)	71 MZM, 74 MZF	11.1(0.25)	?	White	Male	0.66	0.64
	23 DZM, 31 DZF, 52 DOS				Female	0.66	0.51
McIlhany et al. (1974)	40 MZM, 47 MZF 32 DZM, 36 DZF, 45 DOS	14.0(6.5)	5.0–50.0	B&W	Male Female	0.41 0.78	0.56 0.61
Snieder et al. (2003)	75 MZM, 91 MZF	14.9(3.0)	10.0–26.0	White	Male	0.57	0.45
	33 DZM, 31 DZF, 78 DOS	14.6(3.2)	10.0–26.0		Female	0.57	0.45
	52 MZM, 58 MZF			Black	Male	0.57	0.58
	24 DZM, 39 DZF, 50 DOS	Female	0.57		0.58		
Snieder et al. (1995)	35 MZM, 33 MZF 31 DZM, 29 DZF, 28 DOS	16.8(2.0)	13.0–22.0	White	Male Female	0.49 0.66	0.69 0.50

Abbreviations: *MZF* monozygotic females, *MZM* monozygotic males, *DZF* dizygotic females, *DZM* dizygotic males, *DOS* dizygotic opposite sex, *B&W* black and white combined, *M&F* males and females combined

<sup>a</sup>Range of heritability estimates between 2 months and 1 year are given

<sup>b</sup>Heritability estimates reported by Levine et al. (1982) were doubled as outlined by Kramer (1984)

more surprising that environmental factors shared within families, such as salt intake or physical exercise, apparently explain a negligible amount of variation in BP. Part of the explanation might be that even apparently environmental variables such as diet and exercise have a heritable component (de Castro 2001; De Geus et al. 2003; Simonen et al. 2002). Another reason might be that many twin studies may lack the power to detect moderate size influences of common environment (Hopper 2000; Middelberg et al. 2002). A few studies that either had large sample sizes (Hong et al. 1994; Snieder et al. 2000) or used a more powerful multivariate approach (Boomsma et al. 1998) did find a small contribution of shared environment of around 10–20%. The conclusion seems nevertheless warranted that, if not entirely, the familial aggregation of BP is still largely due to genes rather than environmental factors shared within the family.

### Sex Effects on BP Heritability

The existence of sex differences (sexual dimorphism) in the influences of genetic and environmental factors on the phenotype can take several forms. Although autosomal genes are not expected to be different between males and females as a result of the random nature of chromosomal segregation during meiosis, it is possible that some genes (or environments) have greater impact in women than in men (or vice versa), or that some genes contributing to BP in women are distinct from genes contributing to BP in men (Reynolds and Hewitt 1995). Sex differences in magnitude of genetic and environmental effects can be tested by comparing parameter estimates between males and females. If studies considered sex differences in heritabilities, estimates for males and females are listed separately in Tables 1 and 2. However, heritability estimates for males

**Table 2** Adult twin studies estimating heritability ( $h^2$ ) in systolic (SBP) and diastolic blood pressure (DBP), in ascending order according to age

Study	Pairs of twins	Age		Race	Sex	$h^2$	
		Mean (SD)	Range			SBP	DBP
Sims et al. (1987)	40 MZM, 45 DZM	19.4 (3.0)	?	White	Male	0.68	0.76
Ditto (1993)	20 MZM, 20 MZF 20 DZM, 20 DZF, 20 DOS	20.0 (5.0)	12.0–44.0	White	Male Female	0.63 0.63	0.58 0.58
McCaffery et al. (1999)	129 MZ, 66 DZ	21.3 (2.8)	18.0–30.0	94% white	M&F	0.48	0.51
Bielen et al. (1991)	32 MZM	21.7 (3.7)	18.0–31.0	White	Male	0.69	0.32
	21 DZM	23.8 (3.9)					
Fagard et al. (1995)	26 MZM	23.8 (4.2)	18.0–38.0	White	Male	0.64	0.73
	27 DZM	24.7 (4.8)					
Busjahn et al. (2000)	100 MZ, 66 DZ	29.8 (12.0)	?	White	M&F	0.74	0.72
Slattery et al. (1988)	77 MZM, 88 DZM	? ( ? )	22.0–66.0	White	Male	0.60	0.66
Vinck et al. (2001)	150 MZ, 122 DZ	34.9 ( ? )	18.0–76.0	White	M&F	0.62	0.57
Jedrusik et al. (2003)	39 MZ, 37 DZ	35.0(8.0)	18.0–45.0	White	M&F	0.53	0.62
Williams et al. (1992)	14 MZM, 44 MZF	36.4 ( ? )	17.0–65.0	White	Male	0.60	0.52
	9 DZM, 31 DZF, 11 DOS				Female	0.60	0.43
Austin et al. (1987)	233 MZF, 170 DZF	42.0 ( ? )	?	90% white	Female	0.35	0.26
Baird et al. (2001) <sup>a</sup>	30 MZM, 28 MZF	43.7 (1.4)	40.5–46.5	White	Male	0.48	0.30
	35 DZM, 45 DZF, 60 DOS				Female	0.48	0.76
Snieder et al. (1995)	43 MZM, 47 MZF	44.4 (6.7)	34.0–63.0	White	Male	0.40	0.42
	32 DZM, 39 DZF, 39 DOS				Female	0.63	0.61
Snieder et al. (2000)	213 MZF, 556 DZF	45.4 (12.4)	18.0–73.0	White	Female	0.17	0.22
Feinleib et al. (1977)	250 MZM, 264 DZM	? ( ? )	42.0–56.0	White	Male	0.60	0.61
Hong et al. (1994)	41 MZM, 66 MZF	63.0 (8.0)	>50.0	White	Male	0.56	0.32
	69 DZM, 111 DZF				Female	0.56	0.32
Wu et al. (2011)	332 MZM, 111 DZM, 288 MZF, 103 DZF, 200 DOS	37.8 (9.8)	19.1–81.4	Chinese	M&F	0.46	0.30
Li et al. (2013)	309 MZ, 447 DZ	38 ( ? )	18–67	White	M&F	0.71	0.64
	183 MZ, 142 DZ	40.5 ( ? )	18–69	Chinese	M&F	0.53	0.52

For abbreviations, see Table 1.

<sup>a</sup>DBP heritabilities were not reported in the original paper

and females are remarkably similar. A number of studies even report the same heritabilities for the two sexes, indicating that estimates for males and females could be set equal as part of the model fitting process used in these studies. Lower

correlations in DZ opposite-sex pairs compared to same-sex DZ pairs indicate that genetic or shared environmental influences may differ in kind between males and females, but this has never been reported for BP.

## Ethnic Effects on BP Heritability

Genetic as well as environmental differences between different ethnic populations may result in different BP heritabilities. As shown in Tables 1 and 2, most twin studies were conducted in Caucasian populations and a few combined twins from different ethnic groups without reporting separate heritability estimates (Levine et al. 1982; McIlhany et al. 1974). To resolve the question whether the relative influence of genetic and environmental factors on BP in youth is different between black and white Americans, we conducted a classic twin study including both ethnic groups living in the same area. In this first study to estimate and compare the relative influence of genetic and environmental factors on BP in a large sample of young black and white twins, heritability estimates of BP in black and white youth were not significantly different (Snieder et al. 2003). Thus, concurrent with the few other twin studies of non-Caucasians as reported in Table 1 and Table 2, there seems to be no evidence for large differences in BP heritabilities between different ethnic groups. The fact that a similar amount of BP variation is explained by genetic factors within different ethnicities does not exclude the possibility, however, that the actual genes responsible for this heritability differ between ethnic groups.

## Twin Studies Using Ambulatory BP

Conventional BP measures have shown their value in predicting adverse outcomes but provide only a snapshot of 24-h BP variability as seen in real life and might give an overestimation of actual BP as a result of the white coat effect. The value of ambulatory BP (ABP) measurements is illustrated by studies showing that ABP is a better predictor of target-organ damage and cardiovascular morbidity and mortality than BP measured in the clinic (Verdecchia 2000).

To circumvent the disadvantages of conventional BP measures, some twin studies have incorporated 24-h ABP monitoring. Initial studies

suggested that 24-hour, daytime and nighttime, SBP and DBP were all heritable, but sample sizes were fairly small (Degaute et al. 1994; Fagard et al. 1995; Jedrusik et al. 2003; Somes et al. 1995).

Subsequently, several twin studies with relatively large sample sizes using ABP monitoring were conducted. Vinck et al. (2001) measured conventional and ambulatory BP in 150 MZ and 122 DZ pairs. Heritabilities were similar (around 50%) for resting and ambulatory (daytime and nighttime) SBP and DBP irrespective of the chorionicity of the MZ twins, i.e., whether these had one (monochorionic) or two (dichorionic) outer fetal membranes (Fagard et al. 2003). Kupper et al. (2005) evaluated daytime ABP in 230 MZ, 305 DZ twins, and 257 singleton siblings with an average age of 31 years. A common genetic influence on morning, afternoon, and evening SBP and DBP was identified with the heritability ranging from 0.44 to 0.63. Importantly, by using the extended twin design (including singleton sibs), this study showed that results from twin studies on the genetics of ABP can be generalized to the singleton population.

Finally, we measured 24-h ABP in 240 white American (105 pairs and 30 singletons) and 190 black American (82 pairs and 26 singletons) twins (mean  $\pm$  SD age,  $17.2 \pm 3.4$ ; range, 11.9–30.0) from the Georgia Cardiovascular Twin Study (Wang et al. 2009). Inspired by evidence from prospective studies showing that nighttime BP is superior to daytime BP as a predictor of cardiac mortality (Fagard et al. 2008), we performed a bivariate analysis to test whether genetic influences on BP during nighttime are different from those during daytime. The model fitting showed no ethnic or gender differences for any of the measures, with heritabilities of 0.70 and 0.68 for SBP and 0.70 and 0.64 for DBP at daytime and nighttime, respectively. The bivariate analysis also indicated that about 56 and 33% of the heritabilities of nighttime SBP and DBP, respectively, could be attributed to genes that also influenced daytime levels. The specific heritabilities due to genetic effects only influencing nighttime values were 0.30 for SBP

and 0.43 for DBP. We confirmed these findings observing very similar results in an independent large twin study, the Prenatal Programming Twin Study from Belgium, with ABP recorded in 703 twins aged 18–34 (Xu et al. 2015). These findings suggest that a substantial part of the genes or sets of genes contributing to blood pressure regulation at nighttime are different from those during the day.

Nocturnal BP fall (often called dipping) is another interesting feature revealed by ABP. Studies have shown that individuals with a blunted nocturnal decline in BP (so-called non-dipping) display the highest cardiovascular risk because this pattern exposes these individuals to a greater BP load each day. Fava et al. (2005) explored the genetic influence on nocturnal BP fall indexed by the night-to-day ratio and observed a heritability of 38% for systolic and 9% for diastolic dipping in 104 adult Swedish sibships. In our own study mentioned above, we used a liability threshold model to examine whether dipping as a categorical phenotype is heritable and observed a heritability of 59% for SBP dipping and 81% for DBP dipping (Wang et al. 2009).

In addition to mean BP levels, researchers have also examined BP variability (BPV), which is generally estimated by the SD of BP assessed by 24-h ABP. Increased 24-h BPV or nighttime BPV has been shown to be associated with a greater degree of target-organ damage (Parati et al. 1987), cardiovascular events (Eguchi et al. 2009; Stolarz-Skrzypek et al. 2010), and carotid atherosclerosis (Kawai et al. 2013). Despite its clinical importance, little is known about the heritability of BPV. We analyzed 24-h ABP data from the Georgia Cardiovascular Twin Study and the Prenatal Programming Twin Study which in total included 1133 individuals (495 twin pairs and 143 singletons) aged 12–34 of both white and black ancestry and observed that the variance in BPV was predominantly determined by unique environment in youth and young adults, although familial aggregation due to additive genetic and/or common environment influences was also identified explaining about 25% of the variance in BPV (Xu et al. 2013).

## Heritability of BP Measured Under Standardized Environmental Challenges

In many studies, blood pressure is measured under certain standardized environmental challenges. For example, BP can be measured under mental or physical stress. One typical way to express reactivity to such challenges is as a change score from baseline levels of BP to the levels attained during the challenge. This cardiovascular reactivity has long been regarded to be a potential contributor to cardiovascular disease risk (Kamarck and Lovallo 2003; Treiber et al. 2003). A propensity toward exaggerated reactivity combined with frequent exposure to stress may lead to allostatic changes in many of the regulatory systems important in cardiovascular disease.

Studies have been conducted to explore whether cardiovascular reactivity is a heritable trait. In 1992 and 1995, Turner and Hewitt (Hewitt and Turner 1995; Turner and Hewitt 1992) reviewed a number of early twin studies that explored the genetic and environmental origins of individual differences in BP reactivity to psychological challenge. Their conclusion was that BP reactivity is substantially heritable. Additional twin studies of cardiovascular reactivity have since confirmed the heritability of BP reactivity, but estimates for DBP and SBP reactivity have been very different across studies for the same task or within the same study across different tasks and have ranged from 0.00 to 0.85.

We performed a meta-analysis on all published studies in twins that assessed BP reactivity to the cold pressor or mental stress tasks. Our results convincingly show that cardiovascular reactivity is substantially heritable, with the pooled heritability ranging from 0.26 to 0.38 for BP reactivity to mental stress and from 0.21 to 0.55 for BP reactivity to the cold pressor task (Wu et al. 2010). One downside of expressing cardiovascular reactivity as a change score is that its heritability reflects an inseparable mixture of genetic and environmental influences already present at rest with those newly emerging during stress. As illustrated further below, these influences can be



separated when analyzing both resting and challenged *levels* (as opposed to a change score) in a bivariate model.

In fact, levels of such a challenged phenotype may be more heritable than its unchallenged counterpart, potentially offering important advantages for gene-finding studies. This principle is illustrated by Gu et al. (2007) who investigated the heritability of blood pressure responses to dietary sodium and potassium intake in 1906 individuals from 658 Chinese pedigrees. The intervention included a 7-day low-sodium diet, followed by a 7-day high-sodium diet and a 7-day high-sodium plus potassium supplement diet. Baseline heritabilities under the natural diet of SBP and DBP were 0.31 and 0.32, respectively. These heritabilities increased significantly to a narrow range of values between 0.49 and 0.52 for both SBP and DBP in all three environmentally controlled dietary conditions. Interestingly, the authors showed that these increases in heritability estimates were caused not only by a decrease in unique environmental (or residual) variance, as might have been expected under environmentally controlled circumstances, but also by an equally large increase in additive genetic variance. Although Gu et al. (2007) did not elaborate on this, such an increase in genetic variance might have been caused by (1) a larger effect during the dietary conditions of the same genes that also affect BP at rest, (2) an emergence of new genetic effects on BP specific to the dietary conditions, or (3) a combination of the two. Bivariate models that include both challenged and unchallenged conditions can distinguish between these possibilities and quantify genetic and environmental effects on levels of the challenged and unchallenged phenotypes.

We used such an approach to investigate BP during a stress challenge and test for the existence of gene-by-stress interaction within the context of a classic twin study (De Geus et al. 2007). Cardiovascular reactivity to stress, measured as the averaged response to a choice reaction time and mental arithmetic test, was assessed for SBP and DBP in 160 adolescent and 212 middle-aged twin pairs. Genetic factors significantly contributed to

individual differences in resting SBP and DBP in the adolescent and middle-aged cohorts (heritabilities between 0.49 and 0.59). The effect of these genetic factors was amplified by stress for both SBP and DBP in the adolescent cohort and for SBP in the middle-aged cohort. In addition, stress-specific genetic variation emerged for SBP in the adolescent cohort. Heritability of stress levels of SBP and DBP ranged from 0.67 to 0.72 in the adolescents and from 0.54 to 0.57 in the middle-aged cohort. On the basis of these results, we concluded that exposure to stress may uncover new genetic variance and amplify the effect of genes that already influence the resting level (De Geus et al. 2007). We confirmed this conclusion based on similar findings in our Georgia Cardiovascular Twin Study (Wu et al. 2013). This has clear implications for gene-finding studies. The genetic variation that emerges exclusively during stress can only be demonstrated in studies that have attempted to measure the stress levels of BP. Genetic variation that is amplified during stress can be detected using resting levels, but the genetic variance, and hence the power of the study, will be larger if stress levels are measured instead.

In comparison with BP measured under standardized challenge or in the office, real-world recordings are of fundamental importance, for if certain responses do play a role in the etiology of cardiovascular disease, it is in the arena of real-world behavioral challenge and everyday psychosocial interactions that they will take their toll. In this regard, the BP data obtained from 24-hour ABP monitoring can represent real-world recordings because the BP data is acquired in subjects who freely go about their normal daily activities, outside the confines of the hospital or laboratory environment.

Based on the Georgia Cardiovascular Twin Study, which includes 238 white American and 186 black American adolescent and young adult twins who have BP measured in the office, under two psychologically stressful conditions, and by 24-h ABP monitoring, we examined to what extent the genetic influences on BP assessed under these three conditions are different from each other. We observed substantial overlap

between genes that influence BP measured in the office, under laboratory stress and during real life. However, significant genetic components specific to each BP measurement also exist. These findings suggest that partly different genes or sets of genes contribute to BP regulation under different conditions (Wang et al. 2011).

### **Influence of Obesity on Familial Aggregation of BP**

At any age, weight is probably the most important correlate of BP. The familial aggregation of BP may therefore to a certain extent be due to the familial aggregation of obesity. Schieken et al. (1992) addressed this question in a pediatric population of 11-year-old twins. They observed significant correlations between SBP and weight ( $r = 0.40$ ) as well as body mass index (BMI) ( $r = 0.29$ ) that could largely be explained by common genes rather than common environmental effects influencing both SBP and weight (or BMI). The percentage of total SBP variance caused by genetic effects common to SBP and weight was 11.2%, for BMI this figure was 8%. No significant correlations between DBP and body size were found. Two further twin studies in adult males (Vinck et al. 1999) and females (Allison et al. 1995) found evidence for a direct effect of BMI on BP rather than an effect of common genes (pleiotropy). Both mechanisms, however, imply that part of the genetic variation in BP can be explained by genes for obesity (Allison et al. 1995).

Significant interactions between genes and obesity on BP reported from candidate gene studies have led to large-scale systematic investigations of gene-obesity interactions. Such gene-obesity interactions are expected to result in different heritability estimates for BP at different obesity levels. We conducted a twin study systematically exploring gene-BMI interaction (Wu et al. 2011) using data from the Chinese National Twin Registry, which included 1243 monozygotic and 833 dizygotic Han Chinese twins aged 19.1–81.4 years. We observed that both common and unique environmental influences on SBP

increased with increasing levels of BMI, resulting in a lower heritability at higher BMI levels, whereas for DBP the heritability remained unchanged at higher BMI levels. The same research question was later explored using 4153 blacks, 1538 Asians, 4013 whites, and 2199 Hispanic Americans from the Family Blood Pressure Program (FBPP) study (Simino et al. 2014). An ethnicity-dependent pattern was observed. With increasing BMI, the heritability of SBP increased linearly in Hispanic Americans and nonlinearly in European Americans. In Asians, heritability of both SBP and DBP decreased linearly. More research in this field is required before a relatively consistent conclusion can be reached.

### **Influence of Birth Weight on Familial Aggregation of BP**

The association between low birth weight and increased BP, although modest, has been well established as shown by a meta-analysis of 34 studies: BP is lower by 1–2 mmHg for every kg increase in birth weight for children, and the effect size increases to about 5 mmHg/kg in elderly people (Law and Shiell 1996). The fetal programming hypothesis states that this association is due to intrauterine malnutrition (reflected by low birth weight), which increases the risk of a number of chronic diseases in later life including hypertension. However, other factors such as socioeconomic status and genetic factors may also explain the inverse relation between birth weight and BP. By studying intrapair differences in twins (i.e., relate intrapair differences in birth weight with intrapair differences in outcome variables), the influence of confounding parental characteristics can be controlled. Furthermore, influence of genetic makeup can be eliminated in MZ twins and reduced in DZ twins. Using this intrapair twin design, Poulter et al. (1999) found that BP tended to be lower among those twins of each pair that were heavier at birth, suggesting that the inverse association between birth weight and adult BP is independent of parental confounding variables. These results also point to the importance of environmental fetal nutrition

factors that are different within twin pairs such as placental dysfunction rather than factors that are the same such as maternal nutrition.

This was confirmed by a later study (Bergvall et al. 2007) in Swedish twins in which a nested co-twin control analysis was performed in 594 DZ and 250 MZ twin pairs discordant for essential hypertension. The odds ratio for hypertension in relation to a 500-gram decrease in birth weight was 1.34 (95% CI, 1.07–1.69) for DZ and 1.74 (95% CI, 1.13–2.70) for MZ twins, which suggests that the association between birth weight and the risk of hypertension is independent of both shared familial environment and genetic factors. On the other hand, there are also studies supporting the possibility that factors shared by twins confound the association between birth weight and blood pressure. For example, Christensen et al.'s study in 1311 pairs of adolescent twins found a decrease in SBP of 1.88 mmHg for every kg increase in birth weight in the overall sample, but a reduction of this effect was observed when intrapair analyses were used (Christensen et al. 2001). This was confirmed by a meta-analysis (McNeill et al. 2004) in 3901 twin pairs in which the decrease in SBP for every kilogram increase in birth weight was  $-2.0$  (95% CI,  $-3.2, -0.8$ ) mmHg in the unpaired analysis but only  $-0.4$  (95% CI,  $-1.5, 0.7$ ) mmHg in the paired analysis. Thus, the association between birth weight and SBP became attenuated when familial factors were controlled for, suggesting they contribute to this association. However, neither study could convincingly show whether this familial confounding had a genetic or shared environmental origin. In summary, the relation between birth weight and BP is probably due to a combination of environmental and genetic factors, but the contribution to the familial aggregation of BP of genes influencing birth weight is likely to be small (Baird et al. 2001).

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### Age-Dependent Genetic and Environmental Effects on BP

BP level changes as a function of age, but this trend is not a simple linear one. The age-specific increase in SBP and DBP suggests that different

(genetic and environmental) mechanisms have their influence on BP in different periods of life. Not only the mean BP but also its population variance has been found to increase from adolescence to adulthood (Snieder et al. 1995). Such an increase in BP variance with age may be due to interindividual variation in the rise of BP over time and can only be explained by an increase in one or more of the underlying variance components, which can be genetic or environmental. Such changes in variance components may imply changes in heritabilities with aging.

## Cross-Sectional Studies

### Twin Studies

In both Table 1 (mean age < 18 years) and Table 2 (mean age > 18 years), studies are listed in ascending order according to age of the twin sample. Such a systematic overview of all studies may reveal any age-dependent trends in heritability, because each study yields heritability estimates representative of its specific age range. However, neither within the adult nor the pediatric age ranges can clear age trends in BP heritability be detected. Two studies in very young twins (Levine et al. 1982; Yu et al. 1990) confirm the conclusions from previously mentioned family studies that familial aggregation is established early in life. These twin studies suggest that this can be ascribed to genetic factors. The abovementioned study of Vinck et al. (2001) specifically investigated the stability of heritable and environmental influences on both conventional and ambulatory BP in three age groups: 18–29, 30–39, and  $\geq 40$  years. Their large sample of 150 MZ and 122 DZ twin pairs had considerable power but found no significant differences in genetic and environmental influences between age groups.

The conclusion seems warranted, therefore, that the relative influence of genetic factors on BP is stable across the life span.

### Family Studies

#### Parent-Offspring and Sibling Correlations

Another approach to investigating the age dependency of genetic and environmental effects is to

compare parent-offspring data with data from siblings or twins. If there is an age-dependent genetic or environmental effect on the phenotype, one would expect the parent-offspring correlation to be lower than sibling or DZ twin correlations, as the latter are measured around the same age. This expectation was confirmed in a review by Iselius et al. (1983). They pooled the results from a large number of studies and arrived at a mean correlation for 14,553 parent-offspring pairs of 0.165 for SBP and 0.137 for DBP. Corresponding values for 11,839 sibling and DZ twin pairs were 0.235 (SBP) and 0.201 (DBP).

If, on the other hand, parents and their offspring are measured at the same age, a rise in parent-offspring correlations toward levels similar to sibling correlations is to be expected. This expectation was supported by data from Havlik et al. (1979), who measured SBP and DBP for 1141 parent pairs aged 48–51. Twenty to thirty years later, blood pressures for 2497 of their offspring were measured. At this time, the offspring were of ages similar to those of their parents when their BPs were measured. Parent-offspring correlations ranged between 0.13 and 0.25 for SBP and between 0.17 and 0.22 for DBP. These ranges were quite similar to the sibling-pair correlations, which were between 0.17 and 0.23 (SBP) and between 0.19 and 0.24 (DBP).

An alternative explanation for the lower parent-offspring correlation compared to the sibling or DZ twin correlation could be the influence of genetic dominance (Hong et al. 1994; Tambs et al. 1992). However, an effect of dominance is hardly ever found for BP, and the similarity between correlations for parents and offspring (who do not share dominance variation) and siblings (who share 0.25 of their dominance variation) in the study of Havlik et al. (1979) also suggests that dominance variation is not important.

Lower values for parent-offspring correlations are also likely to be the main reason for the peculiar finding that heritability estimates derived from family studies (which usually measure pairs of subjects at different ages) are generally lower than those derived from twin studies. Heritability estimates from family studies range from 0.17 to 0.45 for SBP and from 0.15 to 0.52 for DBP (Hunt

et al. 1989; Iselius et al. 1983; Tambs et al. 1992), while estimates from twin studies are typically in the 0.40–0.70 range for both SBP and DBP (Evans et al. 2003; see also Tables 1 and 2).

### Age-Dependent Gene Expression

Two types of age-dependent effect could offer an explanation for the lower parent-offspring correlation compared to the sibling and DZ twin pair correlations. First, the influence of unique environmental factors may accumulate over a lifetime. Such an increase, however, would lead to lower heritabilities with age, which is not supported by the evidence presented in Tables 1 and 2. Second, different genes could influence BP in childhood and adulthood. This possibility is still compatible with the data presented in Tables 1 and 2, as heritability can remain stable across time even though different genes are influential at different times.

The latter possibility is supported by data from Tambs et al. (1993). In a Norwegian sample with 43,751 parent-offspring pairs, 19,140 pairs of siblings, and 169 pairs of twins, correlations between relatives decreased as age differences between these relatives increased. A model specifying age-specific genetic additive effects and unique environmental effects fitted the data well. This model also estimated the extent to which genetic effects were age specific. As an example, the expected correlations for SBP and DBP in relatives with an age difference of 40 years were calculated. For SBP, 62% of the genetic variance at, for example, age 20 and at age 60 is explained by genes that are common to both ages, and 38% is explained by age-specific genetic effects. The same values for DBP were 67 and 33%, respectively. The model used by Tambs et al. (1993) assumes invariant heritabilities for BP throughout life. This assumption proved to be valid for SBP, whereas for DBP a very slight increase in heritability was detected. Using an extended twin-family design (Snieder et al. 1997), including in addition to younger twins and their parents, a group of middle-aged twins of the same age as the parents provided further support for age-specific genetic effects on BP that differ between childhood and adulthood (Snieder et al. 1995).

Models allowing for these effects showed a slightly better fit for both SBP and DBP with genetic correlations across time equal to 0.76 for SBP and 0.72 for DBP. The slightly lower values found by Tambs et al. (1993) (0.62 for SBP and 0.67 for DBP) might be explained by the larger age difference (40 years) in their example, compared to the age difference between parents and offspring in this study (30 years).

## Longitudinal Studies

Although changes in phenotypic variance and their genetic and environmental components (i.e., heritability and environmentality) with age may be detected by comparing cross-sectional family and twin studies conducted in different age groups, only a longitudinal twin study, in which the same subjects are measured repeatedly, is informative about the stability of genetic and environmental factors. Such a study permits examination of two important questions. First, does the magnitude of genetic and environmental influences on the phenotypes of interest change over time? Second, do novel environmental and/or genetic influences on those phenotypes become apparent during the course of development?

To date, four longitudinal twin studies have addressed the potential emergence of new genetic or environmental factors for BP in adult populations. Colletto et al. (1993) analyzed resting SBP and DBP in 254 monozygotic (MZ) and 260 dizygotic (DZ) male middle-aged twin pairs (average age 48 years) and again 9 years later. Using a time series analysis of genetic and environmental components of variation, they found that shared family environmental effects were absent and that specific environmental influences were largely occasion specific. In contrast, genetic influences were in part the same across adulthood (60% of genetic variation at the later ages was already detected in middle age) and in part age specific (the remaining 40% of the genetic variation at later ages was unrelated to that expressed earlier). Despite these changing genetic influences, the estimated heritabilities remained relatively constant across

ages at around 0.50. When the twins were measured again 6 years after the second measurement, the genetic influence had stabilized, with no contributions of additional genes detected. A second study measured 298 same-sex elderly twin pairs at an average age of 65 years and again 6 years later and found that the same set of genes explained all genetic variance in BP across the 6-year follow-up (Iliadou et al. 2002). That is, no evidence was found for new genes being switched on or off at different points in time. This was confirmed in two studies of Dutch and Australian twins (Hottenga et al. 2005, 2006) in which multivariate genetic analyses showed that BP tracking was entirely explained by the same genetic factors being expressed across time.

The above studies did not include the important transition from childhood to adulthood. We, therefore, conducted a longitudinal twin study on BP (Kupper et al. 2006) for the period between 14 and 18 years of age. Resting BP levels were measured twice in >500 pairs of white and black American twins, with an intervening period of 4.1 years. Structural equation modeling on BP showed the emergence of substantial new genetic variance in both ethnic groups. A possible explanation for this emergence of novel genetic effects between ages 14 and 18 years is that hormonal changes after puberty affect the activation and deactivation of genes influencing individual differences in BP regulation.

These results have important implications for gene-finding studies. In current gene-finding efforts for complex traits, large sample sizes are required to reach sufficient statistical power, especially when genome-wide association or linkage designs are used. It would be advantageous to be able to pool data from subjects at different ages on the assumption that the same set of genes underlies BP regulation across the life span. As we stated above, although most longitudinal studies in adults have confirmed this assumption and reported the presence of a single genetic factor explaining variance in BP over time, our study in youth showed that a significant part of the variance was explained by genes newly expressed between 14 and 18 years of age. This means that one should exercise caution pooling adolescent

and adult subjects in large genome-wide linkage or association studies of BP. Further longitudinal twin or family studies with follow-up into adulthood need to determine at what age the genetic component stabilizes (i.e., at what age no further novel genetic effects are expressed).

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### Heritability Estimation Using Unrelated Persons: Genome-Wide Genetic Data

In the past decade, genome-wide association studies (GWAS) have successfully identified numerous genetic loci for common complex traits including for BP and hypertension (see also “Monogenic and Polygenic Contributions to Hypertension”). In addition to the main approach of GWAS, which tests each single nucleotide polymorphism (SNP) individually for an association with the outcome using a very stringent  $P$  value, the GWAS data from SNP arrays can also be used to estimate the genetic relationship between unrelated individuals. The approach calculates to what extent phenotypic similarities between pairs of unrelated individuals can be attributed to their SNP similarity allowing an estimate of the extent to which phenotypic variance can be explained by genetic variance. The method is called genomic-relatedness-matrix restricted maximum likelihood (GREML) and is implemented in the genome-wide complex trait analysis (GCTA) software (Yang et al. 2011). It was first introduced by Yang et al. (2010) and has now been widely applied to many traits and diseases. Different from the heritability estimated from twin and family data which captures the entire genome, the heritability estimated from the genetic relationships of unrelated individuals only reflects the part explained by common SNPs (i.e.,  $h^2_{\text{SNP}} = \text{common SNP heritability}$ ) interrogated by the GWAS SNP arrays.

The GREML-GCTA approach can help to elucidate the genetic architecture of common complex traits. For example, despite the fact that GWAS has identified many loci for BP and hypertension in adults, these loci at most explain 2–3% of the variance of BP. There is no clear consensus on the

sources of this “missing heritability.” Possible explanations include a large number of common variants with small effects, rare variants with large effects, and DNA structural variation. Using the GREML-GCTA approach, Vattikuti et al. (2012) observed a  $h^2_{\text{SNP}}$  of 20% for SBP, which is about 50% of the total SBP heritability, indicating that a large part of the heritability for SBP is hiding rather than missing because of many SNPs with small effects. Studies by Salfati et al. in the ARIC cohort (Salfati et al. 2015) and by Zaitlen et al. in a large Icelandic population (Zaitlen et al. 2013) confirmed these observations that at least half of the SBP and DBP heritability derives from common genetic variants. Further analyses according to function class by Salfati et al. (2015) indicated that these common genetic variations were almost exclusively in noncoding (intronic and intergenic) genomic regions with likely regulatory function affecting gene expression.

A bivariate extension of GREML-GCTA allows estimation of the genetic covariance and hence genetic correlation between different traits and disorders to provide estimates of genome-wide pleiotropy (Lee et al. 2012). These traits or disorders can be collected from the same or from different individuals. For example, Vattikuti et al. (2012) explored the genetic correlation between metabolic traits (measured in the same individuals) using bivariate GCTA and observed large genetic correlations between BMI and waist-hip ratio as well as between triglyceride and high-density lipoprotein. Using GWAS data of different diseases from the Wellcome Trust Case Control Consortium, Lee et al. (2012) observed that the estimated genetic correlation between hypertension and type 2 diabetes was 0.31, indicating shared genetic etiology between these two diseases.

For familial aggregation of BP, especially childhood BP, the GREML-GCTA approach has the potential to shed light on many unsolved questions. For example, univariate GREML in unrelated individuals can provide a detailed picture of the genetic architecture of BP unconfounded by common environmental influences, especially now that the method has been extended to include estimation of dominance variation (Zhu et al. 2015) and the use of whole

genome sequencing data or high-density imputation data that include rare variants (Yang et al. 2015). Bivariate GREML-GCTA analyses can determine the contribution of the genetic components of “environmental” risk factors to the familial aggregation of BP, even for those risk factors usually shared within the family such as smoking and physical activity. Last but not least, bivariate GREML-GCTA analyses in unrelated children and adults can also estimate to what extent the same or different common genetic variants contribute to the stability and change in BP from childhood to adulthood.

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## Summary and Conclusions

This chapter has examined causes of familial aggregation of BP and whether and how underlying genetic or environmental influences, or both, are stable or change across the life span. Different types of genetically informative studies were discussed to shed some light on these questions.

Familial aggregation of BP is largely due to genes rather than familial environment, and heritability estimates are very similar across sex, ethnicity, and modes of measurement but appear higher under environmentally challenged conditions. Genes for obesity and possibly birth weight can explain part of the genetic variation in BP. In twin studies of BP level, no age trend in heritability could be detected. Findings in family studies of lower parent-offspring correlations compared to those for siblings and DZ twins indicate, however, that age may influence genetic or environmental effects on BP level. There are two possible explanations: the influence of unique environmental factors could increase with age, or different genes could influence BP in different periods of life. The lack of an age trend in heritabilities in twin studies is inconsistent with the first explanation, because an increase of unique environmental variance in adulthood, without a commensurate increase in genetic variance, would lower the heritability estimate. On the other hand, the twin data are not inconsistent with the second hypothesis of genes switching on and off with age, because the

overall influence of genes can remain stable even though different genes are responsible for the effect. A number of further studies, including longitudinal studies of both adolescent and middle-aged twins, offer additional support for the second hypothesis that partly different genes affect BP in different periods of life, such as childhood, middle age, and old age.

The study of the genetics of mechanisms involved in BP regulation in children might bring us closer to discovering causal mechanisms. There is a considerable tracking of BP levels from childhood to adulthood (Chen and Wang 2008; Li et al. 2009; van Lenthe et al. 1994), making BP at a young age an important predictor of adult levels (Bao et al. 1995). Longitudinal studies that follow children into adulthood can be used to study the influence of candidate genes for BP on the developmental trajectory of BP. Identification of these genes conferring susceptibility to development of essential hypertension in the general population will provide new avenues for treatment and prevention of this debilitating disease (Imumori et al. 2005; Snieder et al. 2002).

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## Cross-References

- ▶ [Monogenic and Polygenic Contributions to Hypertension](#)

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## Abstract

The prevalence rates of high blood pressure and cardiovascular risk have increased in youth, given increasing rates of overweight and obesity. Dietary electrolytes influence blood pressure (BP) mechanisms in youth, and previous research indicates that dietary sodium, potassium, and calcium have clinically important effects on BP regulation. Electrolyte balance is essential for health, and the beneficial effects of decreasing sodium intake on BP in youth have been strongly supported. Though interventional studies demonstrate that reduced intake of sodium is beneficial for BP, it is not clear whether children and adolescents can adhere to long-term efforts to reduce sodium intake. There is a growing body of evidence that increased potassium and calcium intake also reduces the risk of high BP in youth, and studies suggest that some youth may be more likely to adhere to diets that emphasize adding foods (e.g., foods containing potassium and calcium) rather than eliminating foods as is the case with a reduced sodium diet. The purpose of this chapter is to summarize the nutritional electrolyte-related determinants of blood pressure in children and adolescents,

specifically the roles of dietary sodium and potassium in regulating casual BP, BP reactivity, and circadian BP patterns in youth.

## Keywords

Electrolytes • Blood pressure • Children • Dietary sodium • Dietary potassium

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## Introduction

Although the prevalence of hypertension (HTN) is relatively low during childhood and adolescence (Sinaiko et al. 1989), an estimated 2.6–3.4% of youth have hypertensive blood pressure (BP) levels, and 5.7–13.6% have pre-hypertensive BP levels (Muntner et al. 2004, Osthega et al. 2009). BP patterns tend to track

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from childhood to the third and fourth decades of life (Sinaiko et al. 1989, Lauer and Clarke 1989), and elevated BP has been associated with increased risk of cardiovascular and renal disease (Berenson et al. 1993). The prevalence of hypertension and, along with it, presumed cardiovascular risk have also increased given growing rates of overweight and obesity among youth, with studies showing that obese girls have six times the rate of HTN compared to nonobese girls (Obarzanek et al. 2010). Thus, there is a strong need for prevention programs to reduce these risks in youth (Berenson et al. 1993; Chioloro et al. 2007; Zhu et al. 2008). Modifying intake of dietary electrolytes such as sodium and/or potassium has been an effective approach to BP reduction in adults (Carvalho et al. 1989; Whelton et al. 1997; Pietinen et al. 1988), but there is less evidence for the benefit of this approach in children and adolescents (Sinaiko et al. 1993).

Recommendations for the primary prevention of HTN from the American Heart Association, the American Academy of Family Physicians, and the National Heart, Lung, and Blood Institute (Riley and Bluhm 2012; American Heart Association 2014; Whelton et al. 2002; Appel et al. 2006; Falkner and Daniels 2004; American Heart Association 2012) promote a population approach and an intensive strategy for targeting people at increased risk for developing HTN in early adulthood. Two of these approaches include reducing sodium intake and maintaining an adequate intake of potassium. Globally, sodium consumption among children and adolescents exceeds intake recommendations, with cereals, meat products, and fast foods contributing to the problem (Brown et al. 2009). HTN may be further prevented by addressing obesity through weight reduction programs that incorporate physical activity as regular aerobic activity and is strongly recommended as strategies to improve BP (Alpert and Wilson 1992; Borghi et al. 1986; Sica and Wilson 2001; Stabouli et al. 2011; Riley and Bluhm 2012; American Heart Association 2014).

Identifying precursors or markers of HTN in youth is acknowledged as important for preventing the development of primary HTN. Two such markers include cardiovascular reactivity

(CVR) and ambulatory BP profiles (Alpert and Wilson 1992; Borghi et al. 1986; Sica and Wilson 2001). Cardiovascular reactivity is a measure of vasoconstriction in response to psychological or physical stressors. As a marker, high reactivity is a consequence of preexisting cardiovascular damage or of heightened sympathetic tone that results in vasoconstriction and/or excessive cardiac output. As a mechanism, hyperreactive BP peaks are proposed to contribute to arteriosclerosis and subsequent HTN by damaging the intimal layer of arteries. Although there is controversy about the predictive value of measured CVR, prospective studies have shown that increases in CVR by mental stress is predictive of later development of primary HTN (Borghi et al. 1986; Matthews et al. 2004; Masters et al. 2004; Roemmich et al. 2007; Barbeau et al. 2003; Westmaas and Jamner 2006), although efforts to associate increased CVR with physiological correlates of HTN (i.e., left ventricular hypertrophy) have yielded mixed results (Alpert and Wilson 1992; Kaneda et al. 2005; al'Absi et al. 2006; Moseley and Linden 2006; Stewart et al. 2006). Researchers have assessed the relation between adolescent dietary intake and clustering of cardiometabolic risk in 1,369 girls using data from the National Heart, Lung, and Blood Institute Growth and Health Study (Moore et al. 2016). Youth were tracked until they were 17 years old, and findings showed that at the end of adolescence, 35% had developed evidence of at least two cardiometabolic risk factors, and 18% had at least three. Results revealed that adolescent girls who reported high intakes of dairy, fruits, and non-starchy vegetables were almost 50% less likely to have three or more cardiometabolic risk factors in late adolescence. Thus, the study highlights the potential benefits of healthy eating patterns in early adolescence which appear to influence later adolescence cardiometabolic risk.

Ambulatory BP profiles serve as another marker and potential predictor or risk factor for HTN in youth. Ambulatory BP monitoring (APBM) is a method for assessing a person's daily fluctuations in BP and for linking these fluctuations to factors associated with individual differences in BP responses to the natural

environment. Previous research indicates that most people have lower BP values at nighttime during sleeping hours and higher BP values during waking hours (Sica and Wilson 2001). In healthy persons, average BP declines by 10–15% or more during sleeping hours. While this circadian rhythm is generally preserved in hypertensive patients, the 24-h BP profile is shifted upward throughout the 24-h period (Verdecchia et al. 1997). When BP does not decline by at least 10% from waking to sleeping, the circadian pattern is considered blunted, or “non-dipping,” and is associated with greater cardiovascular risk (Sica and Wilson 2001). For example, ambulatory BP non-dipping status is a risk factor for the development of end-organ disease in patients with primary HTN – non-dippers have been reported to suffer more frequent occurrences of stroke and left ventricular hypertrophy (LVH) (Kobrin et al. 1984; Verdecchia et al. 1990; Devereux and Pickering 1991). Even among healthy African-American adolescents, Wilson et al. found that there is a 30% prevalence rate of non-dipping status (Wilson et al. 1996; Wilson et al. 1999c), and other investigators have shown that racial differences in sodium excretion may be due in part to renal retention of potassium (Palacios et al. 2010). These findings have led to investigation of electrolytes in the diet that may influence the ambulatory BP pattern in youth.

Previous research indicates that dietary intake of electrolytes such as sodium, potassium, and calcium significantly affects BP in adults, especially in industrialized countries (Espeland et al. 2002; He and MacGregor 2006; Savoca et al. 2007; Leong and Kainer 1992). Electrolytes are positively and negatively charged ions that moderate the conduction of electrical signals between cells and influence homeostasis within the body (Allison 2004). Appropriate electrolyte balance (i.e., balance of positively and negatively charged conductive ions) is essential for health (Espeland et al. 2002). Previous studies indicate that environmental and genetic factors can influence BP responses in children (Ge et al. 2009; Tobin et al. 2008; Kojima et al. 1994; Weinberger et al. 1987). Some children as young as 0–3 years of age may already be at higher risk for future cardiovascular

complications because their sodium handling is aberrant (Guerra et al. 1997), and stress-induced excretion is a heritable phenotype which differentially affects African-Americans as compared to Caucasians (Ge et al. 2009; Hanevold et al. 2008). Other investigators have demonstrated that salutary changes in dietary electrolytes instituted in the first two decades of life can reduce BP and cardiovascular risk across the lifespan (He and MacGregor 2006; Savoca et al. 2007; Couch et al. 2008; Cook et al. 2009). The beneficial effects of decreasing sodium intake on BP have stronger support than the effects of increasing potassium, and few studies have actually evaluated the influence of potassium on BP levels in youth (Simons-Morton and Obarzanek 1997).

This chapter will summarize the dietary electrolyte-related determinants of BP in children and adolescents. In particular, the chapter focuses on the role of dietary sodium and potassium in regulating casual BP, BP reactivity, and circadian BP patterns in youth. While not a focus of this chapter, the role of calcium intake on BP will also be noted. Several investigators have demonstrated protective effects of calcium supplementation on BP (van Mierlo et al. 2006) and in youth (Gillman et al. 1995; Mu et al. 2009; Simons-Morton et al. 1997; Sugiyama et al. 2007; Dwyer et al. 1998).

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## Dietary Sodium and Blood Pressure in Youth

Previous research suggests that casual BP level is important in understanding the influence of genetic, environmental, and nutritional factors on the progression and development of HTN in children and young adults. In a national study of 1,658 youth (ages 4–18 years), He and MacGregor showed a significant association between sodium intake and systolic BP after adjusting for age, sex, body mass index (BMI), and dietary potassium intake (He and MacGregor 2006). Additionally, Yang et al. (2012) assessed the association between normal sodium intake and blood pressure in 6,235 children and adolescents aged 8–18 years (51% male) taking part in the National Health and Nutrition Evaluation Survey

(2003–2008) and revealed that sodium intake was positively associated with systolic BP levels and with risk for HTN. Additionally, they found that this relation was stronger in overweight or obese youth. The magnitude of the association was similar to that observed in a meta-analysis that evaluated the effects of sodium reduction on BP responses in youth (Simons-Morton and Obarzanek 1997) in which 25 observational studies examining the association between sodium intake and casual BP in children and adolescents were critically evaluated. Eight of the included studies used self-reported measures of dietary intake, and 17 used urinary sodium excretion as a surrogate for sodium intake. Two-thirds (67%) of the studies that included urine collections and controlled for other factors (e.g., age, BMI, weight) in the analysis found a significant positive association with casual BP levels. Three of the four studies that relied on self-reported measures of dietary intake and that controlled for other variables found significant positive associations between dietary sodium and casual systolic BP, diastolic BP, or both. Taken together, the studies reviewed for the meta-analysis provide fairly consistent support for a role of sodium intake on BP regulation in children and adolescents. Thus, interventions that reduce the dietary intake of sodium may be beneficial, although it is not clear whether children and adolescents can adhere to long-term recommendations to reduce sodium intake.

Prior research shows that people at risk for cardiovascular complications such as African-Americans, hypertensive patients, and persons with a positive family history of HTN are a priori more likely to be salt sensitive, i.e., to have an increase in BP in response to high sodium intake (Weinberger et al. 1986; Falkner et al. 1986). Wilson et al. (1999a) examined the prevalence of salt sensitivity in normotensive African-American adolescents and characterized 22% of healthy normotensive African-American adolescents as salt sensitive based on their results using definitions established in the adult literature (Sullivan and Ratts 1988). Falkner et al. have also shown that salt-sensitive adolescents with positive family history of HTN had greater increases in BP with salt

loading than did adolescents who either were salt resistant or had a negative family history of HTN (Falkner et al. 1986). In another study by Palacios et al., African-American girls showed greater sodium retention in response to a low sodium diet (57 mmol/day) than Caucasian girls. Taken together, these data suggest that differences in sodium handling may contribute to underlying racial differences in susceptibility to developing HTN (Palacios et al. 2004).

Several investigators have also examined the relation between salt sensitivity and ambulatory BP profiles in children and adolescents who are normotensive. Wilson et al. (1999b) examined ABPM patterns in normotensive African-American adolescents and found that a significantly greater percentage of salt-sensitive adolescents were classified as non-dippers according to mean BP (<10% decrease in BP from awake to asleep) as compared to salt resistant. These findings are consistent with other investigators' findings, which have shown that awake BP is elevated in normotensive salt-sensitive versus salt-resistant adults (de la Sierra et al. 1995), and with earlier findings that sodium intake is an important determinant of ambulatory BP profiles in African-American children and adolescents (Harshfield et al. 1991a).

Researchers have also investigated the observed direct association of salt intake and obesity, while controlling for energy intake (Ma et al. 2015). In a cross-sectional study, Ma and colleagues included 458 adolescents (52% boys) from the UK National Diet and Nutrition Survey. Results showed that an increase in one gram of sodium was associated with a 28% increase in the risk for obesity after controlling for health behaviors including energy intake and physical activity, as well as other demographic factors (Ma et al. 2015). Further, Woodruff et al. assessed the associations of blood pressure, sodium intake, and body weight status in 1,008 seventh grade students (52% male) in Ontario, Canada, school districts (Woodruff et al. 2014). They found that participants who had higher systolic and diastolic BP and higher sodium intake (after controlling for gender and ethnicity) were more likely to be overweight or obese. They argued that these results

suggest a potential need for continued education about maintaining a balanced diet and also demonstrate that BP screening may be useful for health promotion strategies in adolescents (Woodruff et al. 2014). Rocchini et al. conducted a series of studies in obese and nonobese adolescents asking whether BP was sensitive to sodium intake (Rocchini et al. 1989a). Obese adolescents showed greater decreases in casual BP measurements after a shift from high to low sodium intake as compared to nonobese adolescents. The BP sensitivity to the alteration of sodium intake correlated directly with plasma insulin concentration and with hyperinsulinemia (Rocchini et al. 1989a). Such an association has led to speculation that sodium retention might be a mechanism underlying the higher concentrations of plasma insulin in obese adolescents. In another study by Lurbe et al. (2000), 85 obese and 88 nonobese children (ages 3–19 years) underwent 24-h ABPM, and urinary sodium excretion rates were determined. There was an inverse correlation between sodium excretion and weight, suggesting a smaller rate of change in BP by sodium unit among obese as compared to nonobese participants. Additionally, obese participants in the Lurbe et al. (2000) study had higher recorded ambulatory BP levels associated with the same levels of sodium excretion as compared to non-obese participants. In summary, these studies suggest that obesity may be associated with abnormal sodium regulation, in that obese youth are more likely to be sensitive to alterations in sodium intake than nonobese children.

The link between salt sensitivity and non-dipping status has been more comprehensively examined and understood in adults as compared to children and adolescents (Verdecchia et al. 1990; Devereux and Pickering 1991). Uzu et al. (1997) found that non-dipper nocturnal BP in salt-sensitive patients was normalized to a dipper pattern (drop from awake to asleep) with sodium restriction. Higashi et al. (1997) reported that nocturnal decline in mean BP was significantly smaller in salt-sensitive patients with hypertension when compared to salt-resistant patients with hypertension during a sodium-loading protocol.

The mechanism by which sodium sensitivity alters nighttime BP likely involves the sympathetic nervous system (SNS). For example, SNS arousal has been associated with differential handling of sodium following a behavioral challenge (video games) among adolescents who retain sodium (as demonstrated by having little excretion of sodium into the urine) (Harshfield et al. 1991b). For more discussion see related references (Harshfield et al. 1991a; Light et al. 1983). Additionally, in healthy children, sleep deprivation has been associated with natriuresis and excessive diuresis, as well as with higher nighttime BP and heart rate (Mahler et al. 2012), which indicates another potential pathway through which SNS arousal may impact BP.

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## Dietary Potassium and Blood Pressure in Youth

The beneficial effects of decreasing sodium intake on BP have been more strongly supported than the effects of increasing potassium intake; however, there is growing evidence that an increase in potassium intake has a salutary effect on BP levels in youth. For example, Simons-Morton and Obarzanek (1997) reviewed dietary intake and its influence on BP. For the section of their review concerning potassium and BP, they discussed 13 observational studies that had used various methods to examine the association of potassium intake and casual BP in children and adolescents. Nine of those studies had used urinary measures of potassium excretion, and six of those nine studies also controlled for other factors such as weight. Two of those six studies that controlled for factors beyond potassium intake reported a significant inverse relation between potassium intake and casual BP, while three studies showed none. Further, one of those six studies reported an unexpectedly positive association between potassium intake and casual BP. Four observational studies estimated potassium intake using dietary intake rather than urinary potassium excretion. Two of those relied on self-reported estimates of potassium intake and found a significant inverse relation between potassium intake and systolic or



diastolic BP, while two of those four found no relation. Taken together, these various studies suggest that high potassium has a beneficial effect on casual BP levels in youth. However, as previously noted (Wilson et al. 1999c), the effects of potassium may be most pronounced among salt-sensitive persons, for example, African-Americans, or those with a positive family history of HTN. Salt sensitivity was not specifically addressed in Simons-Morton and Obarzanek's paper (1997).

Research examining the effects of potassium intake on CVR has been limited. In general, available studies have been associational and have found beneficial effects only in subgroup analyses. For example, Berenson and colleagues (1979b) reported that African-American boys with the highest BPs and who had clinically significant increases in BP reactivity had lower urinary potassium excretion than Caucasians. Among adult populations, Morgan et al. (1984) demonstrated in hypertensive patients that potassium supplementation (48 mmol/24 h) prevented the increase in BP produced by postural changes. Buendia et al. (2015) considered the longitudinal effects of sodium and potassium intake in 2,185 black and white adolescent girls residing in California, Ohio, and Washington, D.C., during a 10-year period. Interestingly, they found no evidence that higher sodium intake was associated with higher BP. However, they did find that higher intake of potassium inversely affected BP in adolescent girls, highlighting the potential importance of consuming potassium-rich foods in adolescence (Buendia et al. 2015).

Few studies have characterized the relation between plasma potassium and ambulatory BP. In a study of adults, Goto et al. (1997) observed a significant negative association between daytime plasma potassium concentration and 24-h systolic and diastolic BPs in patients with primary HTN. Plasma potassium was also inversely correlated with daytime and nighttime systolic and diastolic BP levels. Interpreting the relation between a plasma electrolyte such as potassium and BP is difficult, however, because there are many factors that may influence plasma potassium values (Solomon et al. 1991; Struthers

et al. 1983). Although there are limitations of accuracy with plasma potassium values, these results are consistent with prior epidemiological studies, which have shown associations between potassium intake, potassium excretion, and BP levels (Linas 1991).

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## Nutritional Interventions and Blood Pressure in Youth

A number of studies have examined the prevalence of consumption of high-potassium/low sodium foods (e.g., fruit and vegetable intake) among adolescent populations. In a report by Falkner and Michel (1997), the average sodium intakes of urban children and adolescents in Philadelphia substantially exceeded their nutritional needs, determined by 24-h dietary recall assessments. These findings are consistent with results from the Bogalusa Heart Study, which also assessed electrolyte intake among infants and children living in a rural biracial community (Frank et al. 1988). In another study by Pomeranz et al. (2002), increased BP levels were found among infants at 6 weeks of age who received formula mixed with high sodium tap water (196 mg/l), compared to infants who received formula mixed with low sodium mineral (32 mg/l). One randomized controlled trial carried out in Gambia, West Africa, examined the impact of maternal calcium supplementation during pregnancy on later BP in offspring at age 5–10 years; at the time BP was assessed in the offspring, there was no relation to whether the mother was or was not supplemented (Hawkesworth et al. 2011).

In a study of older youth, Cullen et al. (1999) found that potassium intake based on reported fruit consumption during high school declined overall for 5,881 male and female adolescents and young adults (aged 14–21). Consistent with that finding, Neumark-Sztainer et al. reported that of 30,000 adolescents who completed the Minnesota Health Survey and who had inadequate potassium intake, 28% had inadequate fruit intake, and 36% had inadequate vegetable intake (Neumark-Sztainer et al. 1998). Several investigators, including Berenson et al. (1979a), reported

that African-American children and adolescents have had lower urinary potassium excretion rates than same-age Caucasians (Harshfield et al. 1991a; Pratt et al. 1989). Thus, targeting adolescents, particularly minority adolescents, for dietary interventions that would emphasize high-potassium/low sodium food choices may be an important recommendation.

Dietary electrolytes such as sodium, potassium, and ratio of sodium/potassium in the diet are important in BP regulation. A number of studies have examined the influence of altering electrolyte intake on BP responses in children and adolescents. Tables 1 and 2 provide a summary of the interventions in youth that have studied the effects of either reduced sodium intake, increased potassium intake, or combination on BP responses. In general, the evidence is inconsistent but suggests that reducing sodium intake and increasing potassium intake may be effective strategies. However, further research is needed to determine the long-term adherence to such interventions in youth.

He and MacGregor (2006) did a meta-analysis that included ten trials in children and reported that sodium reduction (ranging from 42% to 54%) led to prompt decreases in BP. In a study by Miller et al. (1988), the effects of sodium restriction for 12 weeks (60 mEq/24 h) on BP responses in Caucasian youth ages 3–30 years were evaluated. They observed a decrease in diastolic BP after adjusting for age, sex, height, and weight; however, the magnitude of change was minimal (–2 mmHg). Other investigators have also failed to demonstrate clinically significant decreases in casual BP in Caucasian children ranging from 4 weeks to 1 year of age during sodium restriction (Gillum et al. 1981; Watt et al. 1985).

Children and adolescents with certain specific risk factors may have more positive BP responses to sodium restriction. For example, Rocchini et al. demonstrated that obese adolescents had significantly greater decreases in mean BP than non-obese adolescents when they went from a high sodium diet to a low sodium diet (Rocchini et al. 1989b). Other researchers have also demonstrated greater reductions to alterations in sodium intake on casual BP responses in African-American

children compared to Caucasian children (Wilson et al. 1992). Interestingly, He et al. (2015) recently performed a cluster randomized controlled trial that utilized 28 primary schools in China. The participating schools were randomized to either interventions where children were taught behavioral skills to reduce the intake of salt. Youth in a second intervention group were taught the behavioral skills and then were taught to instruct their families on the importance of reducing salt intake. The results showed that behavioral skills training was effective in reducing the salt intake for both students and their families and subsequently decreased systolic blood pressure, when comparing the two interventions to the control group (He et al. 2015). Simons-Morton and Obarzanek identified 11 relevant behavioral intervention studies, eight of which used a randomized controlled design that examined the effects of reducing sodium intake on casual BP in children and adolescents (Simons-Morton and Obarzanek 1997). The studies ranged in size from 10 to 191 participants (children and/or adolescents). Duration of the interventions ranged from 3 weeks to 3 years, with half lasting 3–4 weeks. Seven of eleven of the studies reported reduced systolic BP, diastolic BP, or both. However, only four of these studies reported statistically significant effects. Effects were stronger for girls and for those with BMI less than 23 kg/m<sup>2</sup>. One study that directly evaluated the effects of increasing potassium was the Dietary Intervention Study Children (DISC). Participants enrolled had elevated low-density lipoprotein cholesterol. Assessments were done at baseline, 1 year, and 3 years. Longitudinal analyses revealed significant inverse associations between systolic BP and potassium, calcium, magnesium, protein, and fiber and significant inverse associations between diastolic BP and potassium, calcium, magnesium, protein, carbohydrates, and fiber. Direct associations were also found between fat intake and both systolic and diastolic BP. Multivariate models showed calcium, fiber, and fat to be the most important determinants of BP level in children with elevated low-density lipoprotein cholesterol.

Sinaiko et al. (1993) tested the feasibility of potassium supplementation or sodium reduction

**Table 1** Effects of dietary sodium and potassium interventions on blood pressure in youth

Authors	Intervention	Sample baseline demographics	Adherence	Findings
(Whitten and Stewart 1980) United States	Two-group RCT; duration = 5 months/group with 8-year follow-up. <i>Intervention:</i> Low sodium infant diet (LS; $n = 13$ ), commercially available foods without sodium added (1.93 mmol/100 kcal) were provided to parents and fed to infants <i>Control group (CTL; <math>n = 14</math>)</i> Commercially available foods with sodium	$N = 27$ (F = 0, M = 27) Healthy African-American male infants. <i>Age (months) = 3</i> <i>Race = 100% African-American</i> <i>Mean BP = not reported</i>	<i>24-h <math>U_{Na}</math>:</i> samples were collected for 3 days via metabolic frames. Na concentration was 11.3 mmol/day in the LS group and 54.8 mmol/day in the CTL group <i>Food records:</i> records showed a reduction in sodium intake consistent with $U_{Na}$ findings	The LS diet did not result in significant changes in BP in the LS group vs. the CTL, at 8-months (88/48 MBP vs. 90/49 MBP) or 8-year follow-up (103/75 MBP vs. 103/76 MBP). BP was significantly correlated with weight but not sodium intake or sodium or potassium excretion at 8 months
(Gillum et al. 1981) United States	Two-group RCT Duration = 1 year <i>Family education program (FEP; <math>n = 41</math> [children + families])</i> Four biweekly 90-min lectures followed by 90-min maintenance sessions at bimonthly intervals. Educational materials covered physiological and dietary factors involved in BP. Parents were instructed to provide <70 mmol Na/day to each family member <i>Control group (CTL; <math>n = 39</math>)</i> , no treatment	$N = 80$ children + their families (F = 61% FEP; F = 31% CTL) Children with SBP > 95th percentile for age and sex but SBP <130 and DBP <90 mmHg from the Minneapolis, MN public school system <i>Mean age (year) = 7.8 ± 0.7 (FEP); 8.0 ± 0.8 (CTL)</i> <i>Race = not reported</i> <i>Mean BP = 111/65 (FEP); 115/69 (CTL)</i>	<i>Food records (3 days):</i> The FEP group reported significantly lower sodium intake than the CTL group (~25 mmol decrease) <i>24-h <math>U_{Na}</math>:</i> overnight Na excretion did not differ between groups at baseline or 1 year. Poor parent compliance with urine collection method prevented analyses of parental Na excretion	Based on 3 days food record sodium intake for the FEP group was ~25 mmol lower than the CTL group. FEP group participants who regularly attended sessions had sodium intake ~43 mmol lower those who did not attend sessions or who dropped out of the program Urinary sodium excretion did not differ between groups Blood pressure did not differ by group or change over time
(Trevisan et al. 1981) United States	Two-group RCT Duration = 10 weeks/group <i>Low sodium diet (LS; <math>n = 12</math>)</i> Diet included reduction of sodium intake by ~70%	$N = 21$ Male and female students from a boarding high school <i>Age (year) = 11–15</i> <i>Race = not reported</i> <i>Mean SBP</i>	<i>24-h <math>U_{Na}</math>:</i> there was a significant reduction in erythrocyte Na concentration in the LS group but no change in the CTL group. Random samples and	Erythrocyte sodium concentration was reduced, and a nonsignificant decline in SBP was observed in the LS group (−1.25 ± 4.96 mmHg)

(continued)

**Table 1** (continued)

Authors	Intervention	Sample baseline demographics	Adherence	Findings
	<i>Control group</i> (CTL; $n = 9$ ) Diet similar in composition to control but without reduced sodium	(mmHg) = 108 (LS); 111 (CTL)	duplicate meals were collected, but results were not reported	
(Hofman et al. 1983) Netherlands	Two-group RCT Duration = 6 months <i>Low sodium infant formula</i> (LS; $n = 225$ ) Commercially available formula with 33% the concentration of sodium as the control formula <i>Control group</i> (CTL; $n = 241$ ) Commercially available formula with sodium included (9.25 mmol/100 kcal) was provided to parents and fed to infants	$N = 466$ (F = 49%, M = 51%) Newborn infants born within 1 month of each other <i>Age (week) = 1</i> <i>Race = not reported</i> <i>Mean SBP</i> (mmHg) = 88 (LS); 87 (CTL)	<i>Spot <math>U_{Na}</math></i> : Na concentration was 22.7 mmol/L in the CTL group and 11.1 mmol/L in the LS  <i>Baby food delivered</i> : Mean Na consumed based on number of food deliveries was estimated to be 2.5 mol of Na in the CTL group and 0.89 mol of Na in the LS group	The LS formula group demonstrated decrease in SBP at 25 weeks ( $-2.00 \pm 2.13$ mmHg)
(Cooper et al. 1984) United States	Two-group crossover RCT Duration = 24 days/condition <i>Low sodium diet</i> (LS) Diet included reduction of sodium intake by ~ 200–60 mmol/day via controlled cafeteria meals. Children were instructed not to add salt or condiments to meals, and between-meal snacks were provided <i>Control group</i> (CTL) Meals were same as LS group but without reduced sodium	$N = 113$ (F = 66, M = 47) Adolescent students from a boarding high school without HTN or chronic illness <i>Mean age (year) = 16</i> <i>Race = not reported</i> <i>Mean SBP</i> (mmHg) = 109/61	<i>Overnight <math>U_{Na}</math></i> : samples were collected in 42% ( $n = 48$ ) of participants. Na concentration changed from 31 to 13 mmol/8 h. Duplicate meals were collected for 24-h period for three random participants per group per week. Food samples were in close agreement with $U_{Na}$	Sodium intake was reduced by ~ 58% and SBP and DBP decreased nonsignificantly ( $-0.6 \pm 0.70$ mmHg; $-1.40 \pm 1.0$ mmHg) following the LS diet. Participants with BMI below the median had significant decreases in SBP after the LS diet ( $p < 0.05$ ). Body size may influence BP response to sodium reduction

(continued)

**Table 1** (continued)

Authors	Intervention	Sample baseline demographics	Adherence	Findings
(Calabrese and Tuthill 1985) United States	Two-group RCT Duration = 12 weeks/group <i>Low sodium water (LS; n = 51)</i> Bottled water with low sodium water (10 mg/L) was provided to children for drinking and family meal preparation and in school classrooms <i>Control (CTL; n = 102)</i> Bottled water with higher sodium (110 mg/L) was provided to children for drinking and family meal preparation and in school classrooms	$N = 153$ (F = 75, M = 78) Fourth grade school children in a community with high sodium in their water distribution system. Children were matched by sex, school, and baseline BP <i>Mean age (year) = 9</i> <i>Race = not reported</i> <i>Mean BP (mmHg) = 99/58</i>	<i>First-morning <math>U_{Na}</math></i> : Na concentration changed from 141 to 128 mmol/L in the LS group and from 121 to 124 mmol/L in the CTL. No statistically significant differences were detected between boys and girls	BP levels among girls but not boys in the LS group demonstrated decreased BP over time when compared to the CTL group Lack of effects for boys may have been due to undetected poorer compliance in boys or other explanations
(Howe et al. 1985) Australia	Two-group crossover RCT Duration = 3 weeks/condition <i>Low sodium water (LS)</i> Parents and children were interviewed by a dietician who provided detailed instruction on adhering to a low sodium diet <i>Control group (CTL) no treatment</i>	$N = 21$ (F = 48%, M = 52%) Prehypertensive or hypertensive adolescents <i>Mean age (year) = 11–14</i> <i>Race = not reported</i> <i>Mean BP (mmHg) = 119/78</i>	<i>Overnight <math>U_{Na}</math></i> : Na/creatinine ratio changed from 179.1 to 101.7 mmol.24 h <i>Food records</i> : records showed a reduction in sodium intake consistent with $U_{Na}$	Overnight $U_{Na}$ demonstrated a reduction in sodium intake of 43.3%. A slight decrease in DBP was demonstrated ( $-1.3 \pm 1.8$ mmHg)
(Tuthill and Calabrese 1985) United States	Three-group RCT Duration = 12 weeks/group <i>Morning sodium capsule (MS)</i> Participants took one capsule containing 2 g of sodium in the morning and one placebo capsule in the evening each day <i>Evening sodium capsule (ES)</i> Participants took one placebo capsule in the morning and	$N = 216$ (F = 75, M = 78) Ninth through twelfth grade adolescent girls in a private boarding school. Children were matched by sex, school, and baseline BP <i>Mean age (year) = 9</i> <i>Race = not reported</i> <i>Mean BP = 99/57 mmHg</i>	<i>24-h <math>U_{Na}</math></i> : urinalysis indicated that Na excretion was significantly higher in the MS and ES groups compared to the CTL group, and compliance was considered to be high	Though compliance was considered high and drop-out rates were low, between-group differences in BP were not detected in either SBP or DBP

(continued)

**Table 1** (continued)

Authors	Intervention	Sample baseline demographics	Adherence	Findings
	one capsule containing 2 g of sodium in the evening each day <i>Placebo control (CTL)</i> Participants took two placebo capsules each day			
(Tochikubo et al. 1986) Japan	Two-group RC Duration = 10 weeks/group <i>Low sodium counseling and self-monitoring (LS+S; n = 12)</i> Hypertension education and diet counseling including self-monitoring of urinary Cl excretion <i>Low sodium counseling (LS; n = 9)</i> Hypertension education focusing on lowering sodium intake	$N = 197$ (F = 17; M = 180) Borderline hypertensive (BHT) and normotensive (NT) students from six high schools in Japan <i>Age (year) = 15–18</i> <i>Race = not reported</i> <i>Mean SBP (mmHg) = 150.3 ± 9.8</i> (BHT); 117.7 ± 12.2 (NT)	<i>24-h U<sub>Na</sub></i> and <i>UK</i> : mean BHT Na excretion was 211 ± 94, and K excretion was 42.1 ± 16.6. Mean NT excretion was 187 ± 80, and K excretion was 39.5 ± 23.6 Na concentration was significantly higher in the BHT group, and K concentration was significantly lower	The LS group did not reduce blood pressure, but sodium excretion (−52 mEq/day), weight (−1.7 kg), and BP (−12/7 mmHg) decreased significantly in the LS+S group Blood pressure of BHT adolescents may be decreased with dietary education and self-monitoring
(Miller et al. 1988) United States	One-group CT Duration = 12 weeks <i>Low sodium diet (LS)</i> Families were instructed to reduce sodium intake to 60 mmol/day to ensure a reduction to 75 mmol/day. Families were instructed to otherwise maintain usual dietary practices	$N = 149$ (F = 85, M = 64) Normotensive identical twin pairs, siblings, and parents recruited through a research twin panel and local schools <i>Mean age (year) = 9.7 ± 0.4 SEM</i> (F); 10.6 ± 0.7 SEM (M) <i>Race = 100% Caucasian</i> <i>Mean BP (mmHg) = 91/54</i> (F); 95/55 (M)	<i>Weekly U<sub>Na</sub></i> : Na concentration decreased from baseline to 41.1 ± 1.9 mmol/day (F) and 53.5 ± 3.6 mmol/day (M) at the end of the LS diet	In both sexes there was a significant change in sodium excretion ( $p < 0.001$ ) without a change in potassium excretion. For boys there was no change in BP and for girls there was a small but significant decrease in DBP ( $p < 0.05$ ). Results suggest that compliance to modest sodium restriction may not consistently lower BP in normotensive children
(Ellison et al. 1989) United States	Two-group crossover CT Duration = 6 months/conditions: <i>Low sodium diet (LS; 309 students)</i> Diet included reduction of sodium intake by ~15–20% via controlled	$N = 2$ schools (F ~ 51%, M ~ 49%) Male and female students from two boarding high schools in the northeastern USA <i>Mean age (year) = 15</i> <i>Race = ~77% Caucasian</i>	<i>Food records</i> : each subject completed on average 4.5 food records during baseline and follow-up periods. Records showed that mean sodium intake was reduced by 15–20%	SBP significantly decreased during the LS diet (−1.7 mmHg, $p < 0.01$ ), and DBP significantly decreased also (−1.5 mmHg, $p < 0.01$ )

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**Table 1** (continued)

Authors	Intervention	Sample baseline demographics	Adherence	Findings
	cafeteria meals and changes in food purchasing and preparation <i>Control group (CTL; 341 students)</i> Meals were same as LS group but without reduced sodium	<i>Mean BP (mmHg) = 107/64</i>		
(Myers 1989) Australia	Two-group crossover RCT Duration = 2 weeks <i>Low sodium diet (LS)</i> Participants were advised by a dietician to reduce sodium intake ( $77 \pm 37$ mmol/day). Advice was based on previous diet history and 24-h $U_{Na}$ <i>High sodium diet (HS)</i> Participants were advised to increase sodium intake ( $201 \pm 37$ mmol/day). Advice was based on previous diet history and 24-h $U_{Na}$	$N = 23$ (F = 100%; M = 0%) Female sodium sensitive (SS) and insensitive (SI) children and adolescents whose parents were affiliated with a hospital in Newcastle, NSW <i>Mean age (year) = 9</i> (SS); 12 (SI) <i>Race = not reported</i> <i>Mean BP (mmHg) = 108/67</i>	24-h $U_{Na}$ : Na concentration changed from 158 to 66 mmol/24 h	Sodium intake was reduced by 58.2% based on $U_{Na}$ in the LS group. Both SBP and DBP decreased in the LS group ( $-3.74 \pm 2$ mmHg; $-1.70 \pm 2.17$ mmHg)
(Nader et al. 1989) United States	Two-group RCT Duration = 1 year/group <i>Low sodium/low fat diet (LS)</i> Three months of intensive educational group sessions promoting decreased sodium and fat intake and increased physical activity followed by 9 months of maintenance sessions <i>Control group (CTL)</i> no treatment	$N = 206$ families (623 persons) Mexican-American and Caucasian families recruited through 15 matched elementary schools. Families were defined as one or more child in grades five or six and one or more adults in the same household <i>Mean age (year) = not reported</i> <i>Race = 26% Caucasian families; 46% Mexican-American families</i> <i>Mean BP (mmHg) = not reported</i>	<i>Food records, 24-h recall, food frequency questionnaire</i> : LS families reported improved eating habits	Significant differences between the LS and CTL groups ranged from 2.3 to 3.4 mmHg for SBP and DBP in both Mexican-American and Caucasian families Greater changes for dietary behaviors were observed than for physical activity in the LS group, and greater dietary change was reported by Caucasian than Mexican-American families

(continued)

**Table 1** (continued)

Authors	Intervention	Sample baseline demographics	Adherence	Findings
(Rocchini et al. 1989b) United States	Two-group crossover RCT Duration = 2 weeks/condition <i>Low sodium diet (LS)</i> Participants adhered to a 4-day rotating meal plan with meals containing 20–30 mmol/day of sodium <i>High sodium diet (HS)</i> Participants took five sodium chloride tablets in addition to their regular meals The LS diet was formulated to be similar in calorie content as the HS diet	$N = 78$ Obese ( $n = 60$ ) and nonobese ( $n = 18$ ) unmedicated adolescents recruited through pediatricians and school nurses <i>Mean age (year)</i> = $12.5 \pm 0.5$ SEM (obese); $12.5 \pm 0.6$ SEM (nonobese) <i>Race</i> = not reported <i>Mean BP (mmHg)</i> = 125/74 (obese); 106/64 (nonobese)	<i>Food records:</i> records analyzed for 6 randomly selected days during the low sodium diet indicated that obese and nonobese participants had similar sodium intake ( $15.9 \pm 4.5$ vs. $14.8 \pm 2.6$ mmol/day)	Obese adolescents had a significantly greater decrease in mean BP when transitioning from a high sodium diet to a low sodium diet than nonobese adolescents ( $-12 \pm$ mmHg vs. $+1 \pm 2$ mmHg; $p < 0.001$ ) BP in obese adolescents may be more sensitive to sodium intake
(Howe et al. 1991) Australia	Two-group crossover RCT Duration = 4 weeks/condition <i>Low sodium diet (LS)</i> Weekly dietary counseling for both children and parents with low sodium bread provided <i>Control group (CTL)</i> Weekly dietary counseling for both children and parents with salt sachets provided	$N = 100$ (F = 48%, M = 52%) School children representing the top, middle, and bottom deciles of the blood pressure range <i>Age (year)</i> = 11–14 <i>Mean SBP</i> = 115/60 mmHg	<i>First-morning <math>U_{Na}</math>:</i> Na concentration decreased from 175.9 to 101.8 mmol/day in the LS condition <i>Food records:</i> a subset of participants completed records and showed a reduction in Na intake consistent with $U_{Na}$ findings	Sodium intake decreased by ~ 42% in the LS condition and both SBP and DBP declined ( $-97 \pm 0.68$ mmHg; $-0.56 \pm 0.71$ mmHg)
(Gortmaker et al. 1999) United States	Two-group CT Duration = 2 years <i>Eat well and keep moving program (EWKM; n = 6 schools)</i> Classroom teachers gave materials focused on decreasing high-fat foods and television watching and	$N = 14$ schools, 479 students (F = 56% EWKM; F = 61% CTL) Children in grades 4 and 5 from public schools in Baltimore, MD <i>Mean age (years)</i> = 9.2 (EWKM); 9.1 (CTL) <i>Race</i> = 91% African-American <i>Mean BP (mmHg)</i> = 115/60	Compliance not reported	Based on 24-h recall methods, sodium intake did not differ between groups or change over time, though fruit and vegetable intake increased significantly more over time in the EWKM group than the CTL ( $p = 0.01$ )

(continued)



**Table 1** (continued)

Authors	Intervention	Sample baseline demographics	Adherence	Findings
	<p>increasing fruit and vegetable intake and physical activity. The program provided links to school food services and families and wellness training programs to teachers</p> <p><i>Control group (CTL; n = 8 schools)</i></p> <p>No treatment</p>			
<p>(Wilson and Ampey-Thornhill 2001)</p> <p>United States</p>	<p>One-group clinical trial</p> <p>Duration = 5 days</p> <p><i>Low sodium diet (LS)</i></p> <p>Children and families were given guidelines and several food items for maintaining a low sodium diet</p>	<p>N = 184 (F = 101, M = 83)</p> <p>Healthy normotensive, unmedicated African-American adolescents recruited from schools, churches, and local recreation centers in the southeastern USA</p> <p><i>Mean age (year) = 14 ± 1 (F); 14 ± 1 (M)</i></p> <p><i>Race = 100% African-American</i></p> <p><i>Mean BP (mmHg) = 101/56 (compliant F); 5,108/53 (compliant M)</i></p>	<p><i>24-h U<sub>Na</sub></i>: compliance was defined as &lt;50 mEq/24 h during the LS diet. Based on these criteria, 77% of adolescents were compliant (n = 114)</p>	<p>SBP trended toward decreasing in compliant participants but decreases were nonsignificant</p> <p>Compliant girls reported higher levels of familial dietary support, whereas compliant boys reported lower levels of familial dietary support</p> <p>Higher dietary support may be associated with adherence in girls</p>
<p>(Pomeranz et al. 2002)</p> <p>Israel</p>	<p>Three-group RCT</p> <p>Duration = 8 weeks/group</p> <p><i>Low sodium formula (LS; n = 25)</i></p> <p>Infant formula diluted with water with 1.4 mmol/L sodium concentration</p> <p><i>High sodium formula (HS; n = 33)</i></p> <p>Infant formula diluted with water with 8.5 mmol/L sodium concentration</p> <p><i>Control group (CTL; n = 15)</i></p> <p>Infants were breastfed</p>	<p>N = 58</p> <p>Newborn Jewish infants in a university-affiliated hospital. Infants from families with history of HTN excluded</p> <p><i>Mean age (week) = 40 ± 1.3 (LS); 40.2 ± 1.1 (HS); 39.5 ± 1.6 (CTL)</i></p> <p><i>Race = not reported</i></p> <p><i>Mean BP (mmHg) = not reported</i></p>	<p><i>Spot U<sub>Na</sub>/creatinine</i>: Na content of the LS group was 57 ± 1.9 mmol and 172 ± 2 mmol for the high HS group. Days of noncompliance were eliminated from analyses</p>	<p>SBP, DBP, and creatinine ratios were significantly greater in the HS group than in the LS and CTL groups. Potassium concentrations were also decreased in the HS group</p> <p>At 24-week follow-up, BP values in the LS group increased toward those of the HS group</p>

(continued)

**Table 1** (continued)

Authors	Intervention	Sample baseline demographics	Adherence	Findings
(Palacios et al. 2004) United States	Two-group crossover RCT Duration = 2 months/condition <i>Low sodium diet (LS)</i> 1 g/day, 43 mmol/day of sodium with fixed amounts of dietary potassium <i>High sodium diet (HS)</i> 4 g/day, 174 mmol/day of sodium with fixed amounts of dietary potassium Packed foods were provided within a 4-days menu cycle and were of the same composition for both groups except for sodium variation	$N = 36$ (F = 100%; M = 0%) Matched African-American ( $n = 22$ ) and Caucasian ( $n = 14$ ) normotensive adolescent females <i>Mean age (year)</i> = 12.4 (African-American); 13.2 (Caucasian) <i>Race</i> = 39% Caucasian, 61% African-American <i>Mean BP (mmHg)</i> = 113/59 (African-American); 113/55 (Caucasian)	<i>24-h <math>U_{Na}</math></i> : Na content of the LS group was $57 \pm 1.9$ mmol and $172 \pm 2$ mmol for the high HS group. Days of noncompliance were eliminated from analyses	Blood pressure significantly decreased ( $p < 0.05$ ) from baseline to the end of the study African-American girls showed greater sodium retention in the HS condition than Caucasian girls though blood pressure did not decrease despite increased sodium retention nor did sodium excretion increase
(Couch et al. 2008) United States	Two-group RCT Intervention = 3 months/group <i>DASH Diet (DASH; n = 29)</i> Initial counseling session with dietician to follow a modified DASH diet. Eight weekly and two biweekly phone calls with interventionists and biweekly mailings <i>Routine care (RC; n = 28)</i> Initial counseling session with dietician encouraging consumption of fruits, vegetables, grains, lean meats, and low fat dairy	$N = 57$ (F = 21, M = 36) Prehypertensive or hypertensive adolescents seeking treatment in a children's hypertension clinic <i>Mean age (year)</i> = $14.3 \pm 2.1$ (DASH); $14.4 \pm 2.1$ (RC) <i>Race</i> = 40 Caucasian, 17 African-American <i>Mean BP (mmHg)</i> = 131/79 (DASH); 126/82 (RC)	Compliance not reported	The DASH group showed a greater decrease in SBP than the RC ( $-7.9\%$ vs. $-1.5\%$ , $p < 0.01$ ) There was an increase for DASH participants in fruit servings among DASH participants, with fruit servings increasing by $\sim 2$ /day and intake of high sodium/fat foods decreasing by $\sim 0.8$ servings/day Intake of potassium and magnesium reportedly increased by 42% and 36% respectively

*BMI* body mass index, *BP* blood pressure, *CT* controlled trial, not randomized, *CTL* control, *DBP* diastolic blood pressure, *F* female, *LS* low sodium diet, *M* male, *HTN* hypertension, *MBP* mean blood pressure, *RCT* randomized controlled trial, *SBP* systolic blood pressure, *U<sub>Na</sub>* urinary sodium

in preventing the rise in BP among adolescents. Adolescents who were in the upper 15th percentile of BP distribution were randomly assigned to potassium chloride supplementation (1 mmol/kg

potassium chloride/day), a low sodium diet (70 mmol sodium/day), or a placebo (normal diet plus placebo capsule). The results demonstrated that both the potassium supplementation and sodium

**Table 2** Effects of dietary potassium interventions on blood pressure in youth

Authors	Intervention	Sample baseline demographics	Compliance	Findings
(Wilson et al. 1996) United States	Two-group RCT Duration = 4 weeks/ group <i>High-potassium diet (HK; n = 20)</i> 80 mmol/d of potassium with four weekly 1-h classes covering education, behavior skills, barriers, and strategies for increasing potassium consumption and feedback on food record keeping and 24-h urine results <i>Usual diet control (CTL; n = 20)</i> Healthy diet program with weekly 1-h classes covering feedback on food record keeping and 24-h urine results	N = 40 (F = 18, M = 22) Healthy normotensive African-American adolescents classified as dippers (>10% BP decrease from waking to sleeping; n = 28) and non-dippers (≤10% BP decrease from waking to sleeping; n = 12) <i>Mean age (year) = 14 ± 1 (dippers); 14 ± 1 (non-dippers)</i> <i>Race = 100% African-American</i> Mean BP (mmHg) = 109 ± 63 mmHg (dippers); 112 ± 61 mmHg (non-dippers)	<i>24-h urinary potassium:</i> collections were obtained at weekly intervals. Urinary K levels increased in the HK group but not in the control group	Awake BP decreased for dippers in the HK group from baseline to posttreatment (119/67–114/64), but increased for non-dippers (115/62–124/67) 75% and 80% of non-dippers switched dipping status in response to the HK diet
(Sorof et al. 1997) United States	Three-group crossover RCT; Duration = 1 week/ condition <i>Potassium solution</i> 1.5 mmol/kg/day <i>Placebo solution</i> cherry syrup <i>CVR stressors</i> blood sampling, cold pressor, video game	N = 39 (F = 33, M = 17) Children ages 7–15 recruited from schools and clinics with (n = 22) and without (n = 17) family history of essential HTN <i>Mean age (year) = 12</i> <i>Race = 44% Caucasian; 56% African-American</i>	<i>12-h urinary potassium:</i> significant increases in K excretion but overnight collections may not have captured compliance for entire week; children complained of unpleasant taste	CVR was not attenuated by the potassium solution compared to placebo. Potassium may need to be supplemented for >1 week to produce positive effects Higher vegetable consumption in Caucasian children than in African-American children was associated with higher urinary potassium/creatinine ratio
(Wilson et al. 1999c) United States	Two-group RCT Duration = 3 weeks/ group <i>High-potassium diet (HK; n = 26)</i> 80 mmol/day of K with four weekly 1-h classes covering	N = 53 (F = 26, M = 27) Salt-sensitive (SS; n = 16) and salt-resistant (SR; n = 37) African-American adolescents. Salt sensitivity was defined as an increase in MBP ≥5 mmHg in transitioning from a low to	<i>24-h urinary potassium:</i> dietary K increase significantly over time in the HK group (p < 0.02), and K levels were significantly higher	At 3-week assessments, all SS and SR participants in the HK group who had been non-dippers (33% and 6%, respectively)

(continued)

**Table 2** (continued)

Authors	Intervention	Sample baseline demographics	Compliance	Findings
	education, behavior skills, barriers, and strategies for increasing K consumption and feedback on food record keeping and 24-h urine results <i>Usual diet control (CTL; n = 32)</i> Diet program; weekly 1-h classes on feedback of diet records and urine results	high sodium diet <i>Mean age (year) = 14 ± 1 (SS); 14 ± 1 (SR)</i>	in the HK group versus the CTL group	achieved dipping status due to decreased nighttime DBP Participants in the CTL group did not show decreases in night time DBP Increased potassium intake did not affect weight or sleep duration
(Wilson et al. 1999b) United States	Two-group RCT Duration = 3 weeks/ group <i>High-potassium diet (HK; n = 26)</i> 80 mmol/day of K with four weekly 1-h classes covering education, behavior skills, barriers, and strategies for increasing K consumption and feedback on food record keeping and 24-h urine results <i>Usual diet control (CTL; n = 32)</i> Healthy diet program with weekly 1-h classes covering feedback on food record keeping and 24-h urine results	<i>N = 58 (F = 30, M = 28)</i> Salt-sensitive (SS; <i>n = 16</i> ) and salt-resistant (SR; <i>n = 42</i> ) African-American adolescents. Salt sensitivity was defined as an increase in MBP $\geq 5$ mmHg in transitioning from a low to high salt diet <i>Mean age (year) = 14 ± 1 (SS); 14 ± 1 (SR)</i> <i>Mean BP (mmHg) = 103/58 (SS); 100/57 (SR)</i>	<i>24-h urinary potassium</i> : dietary K increase significantly over time in the HK group ( <i>p &lt; 0.02</i> ), and K levels were significantly higher in the HK group versus the CTL group	At 3-week assessments, all SS and SR participants in the HK group who had been non-dippers (33% and 6%, respectively) achieved dipping status due to decreased nighttime DBP Participants in the CTL group did not show decreases in night time DBP Increased potassium intake did not affect weight or sleep duration
(Mu et al. 2005) China	Two-group RCT Duration = 2 years/ group <i>Potassium and calcium supplementation (KC; n = 136)</i> Children were took a tablet consisting of 10 mmol potassium and 10 mmol calcium daily	<i>N = 261 (F = 133, M = 128)</i> School children in grades 3–4 with salt sensitivity (SS) and without salt sensitivity (NSS) from Hanzhong, China <i>Mean age (year) ~10.5</i> <i>Race = 100% Asian</i> <i>Mean BP (mmHg) = 103/63 (SS/KC); 103/63 (NSS/KC); 103/63 (SS/CTL); 103/63 (NSS/CTL)</i>	<i>Compliance not reported</i>	Blood pressure was lowered by 4.3–4.8 mmHg for SS children in the KC group, but not for NSS children. Decreases in night sodium excretion in SS children was significantly increased ( <i>p &lt; 0.01</i> ) and was negatively

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**Table 2** (continued)

Authors	Intervention	Sample baseline demographics	Compliance	Findings
	<i>Placebo control (CTL; n = 125)</i> Children took a placebo tablet identical in appearance and taste to the potassium and calcium tablet. All participants were to maintain usual sodium intake			correlated with increase in BP. Moderate increases in dietary calcium and potassium may promote urinary sodium excretion
(Sinaiko et al. 1993) United States	Three-group RCT Duration = 3 years/ group <i>Low sodium diet (LS; n = 70)</i> 70 mmol/day + nutrition counseling seven times during months 1–3 and then trimonthly. Phone calls were made to reinforce instructions <i>Potassium capsule (K; n = 71)</i> 1 mmol/kg/day, double-blind <i>Placebo capsule (CTL; n = 69)</i> Identical to potassium, double-blind	<i>N</i> = 210 (F = 105, M = 105) Minneapolis, MN, public school students in grades 5–8 with SBP >109 mmHg (boys) and 108 mmHg (girls) <i>Mean age (year)</i> = 13.2 ± 0.1 <i>Race</i> = 86.5% Caucasian; 13.5% African-American <i>Mean BP (mmHg)</i> = 114/63 (LS); 114/67 (K); 114/65 (CTL)	<i>24-h UNa</i> : LS group did not achieve 70 mmol/day goal; no change in boys Na excretion (noncompliance); reduced Na excretion in girls from baseline Percentage of expected capsule use: <i>potassium capsule</i> 84.2%, range = 77–93% <i>Placebo capsule</i> 91%, range = 85–97%	No between-group differences were found for boys and BP increased over time For girls in sodium and potassium interventions, BP increased less over time than for placebo groups but did not significantly decrease Differences between boys and girls may be due to poorer compliance in boys Poor compliance in the LS group challenges the feasibility of long-term sodium reduction in adolescents
(Gunther et al. 2009) United States	Cross-sectional study <i>Type 1 diabetes (T1D; n = 2,440)</i> <i>Type 2 diabetes (T2D; n = 390)</i> All participants' diets were analyzed and assessed for concurrence with eight food groups of the Dietary Approaches to Stop Hypertension (DASH) diet for increased fruit and vegetable intake	<i>N</i> = 2,830 (F = 54%, M = 46%) Participants in the SEARCH for diabetes in youth trial ages 10–22 with type 1 or type 2 diabetes <i>Mean age (year)</i> = 14.7–16.6 <i>Race</i> = >71% Caucasian; >5% African-American; >11% Hispanic <i>race T2D</i> = >20% Caucasian; >30% African-American; >14% Hispanic; >12% Native American <i>Mean BP (mmHg)</i> = 108/68	Participants' diets were analyzed using a self-report food frequency questionnaire from which a DASH concurrence score was calculated	In youth with T1D, adherence to DASH was inversely associated with HTN, where as in youth with T2D adherence to the DASH diet was not associated with reductions in the risk of HTN

(continued)

**Table 2** (continued)

Authors	Intervention	Sample baseline demographics	Compliance	Findings
(Mu et al. 2009) People's Republic of China	Three-group RCT Duration = 3 years/ group <i>Low sodium diet (LS;</i> <i>n = 110)</i> Health behavior education given until salt intake decreased to 50–100 mmol per person <i>Potassium + calcium</i> <i>capsule (K+Ca;</i> <i>n = 101)</i> families given supplement and asked to eat as usual <i>Control (CTL;</i> <i>n = 114)</i> families asked to eat as usual	<i>N = 325 (F = 152, M = 173)</i> Chinese adolescents from northwest China with SBP >90th percentile by age and sex <i>Mean age (year) = 20 ± 3.5</i> <i>Race = 100% Chinese</i> <i>Mean BP (mmHg) = 122/75</i> <i>(LS); 124/75 (K+Ca); 124/77</i> <i>(CTL)</i>	<i>24-h UNa:</i> LS achieve 50 mmol/ day and the K + Ca group was compliant	SBP decreased on average by 5.9 mmHg, and DBP decreased 2.8 mmHg in the K + Ca group. In the LS group, SBP decreased by 5.8 mmHg and DBP decreased by 1.0 mmHg Using a salt substitute which contains potassium and calcium may be as effective at reducing BP as sodium restriction

*BMI* body mass index, *BP* blood pressure, *CT* controlled trial, not randomized, *CTL* control, *DBP* diastolic blood pressure, *F* female, *M* male, *HTN* hypertension, *LS* low sodium diet, *MBP* mean blood pressure, *RCT* randomized controlled trial, *SBP* systolic blood pressure, *UNa* urinary sodium

restriction were effective in reducing the rise of casual BP in girls, but not in boys. Such data lead to the questions as to whether long-term restriction of dietary sodium in boys will be successful.

In a study by Couch et al. (2008), the Dietary Approaches to Stop Hypertension (DASH) diet (Sacks et al. 1995) was compared to routine care in a biracial sample of youth. Youth who were randomized to receive the DASH diet (rich in fruits and vegetables, potassium, and magnesium and low in total fat) showed a significantly greater decrease in systolic BP as compared to youth who were randomized to routine care. Those in the DASH diet group also showed significant increases in fruit and vegetable intake, potassium, and magnesium and significant decreases in sodium intake and total fat as compared to the youth in the comparison group over the course of the 12-week intervention. In another study of youth with type 1 and type 2 diabetes mellitus, Günther and colleagues reported that youth with type 1 diabetes who adhered to the DASH diet had lower BPs, independent of demographic, clinical, and behavioral characteristics (Gunther et al.

2009). In contrast, Günther et al. did not find that adherence to the DASH diet was associated with such reductions in the risk of hypertension among youth with type 2 diabetes. Thus, the DASH diet may be a promising approach for improving cardiovascular risk factors such as elevated BP in some youth. Further research is needed to better determine the overall rate of compliance with the DASH diet relative to other approaches to reducing sodium intake and/or increasing potassium intake.

Some evidence suggests that dietary electrolyte intake plays an influential role in circulatory responses to stress. Falkner et al. (1981) conducted a number of investigations to assess how altering dietary sodium affects CVR. In one small study, they evaluated 15 normotensive adolescent girls for 2 weeks, at rest and during mental arithmetic exercises and before and after adding 10 g of sodium to their diet. Those girls with a positive family history of primary HTN showed an increase in resting baseline and stress BP levels. Those girls with a negative family history did not. These findings have been replicated in young adults

(Falkner and Kushner 1990). However, for those young adults with a positive family history of primary HTN, changes from baseline (not from resting) to stress were similar before and after salt loading, with no increase seen due to sodium loading.

Sorof et al. (1997) examined whether CVR was inversely related to the dietary intake of potassium in 39 children (17 Caucasian and 22 African-American). At baseline, the 24-h urinary potassium/creatinine ratio varied inversely with diastolic CVR in Caucasian children with a positive family history of HTN; however, CVR was not attenuated by potassium supplementation (1.5 mmol/kg/day of potassium citrate) compared to placebo. Urinary potassium/creatinine ratio was higher in Caucasian children than African-American children; dietary potassium-modulated CVR in Caucasian children with a family history of HTN but not in African-American children. Consistent with this finding, Wilson et al. (1999c) demonstrated no significant change in BP reactivity in African-American adolescents who adhered to a 3-week high-potassium diet in a study that examined the effects of increasing dietary potassium on BP non-dipping status in salt-sensitive and salt-resistant African-American adolescents. Urinary potassium excretion increased significantly in the treatment group ( $35 \pm 7 - 57 \pm 21$  mmol/24 h). At baseline, a significantly greater percentage of salt-sensitive (44%) adolescents were non-dippers, based on diastolic BP classifications ( $p < 0.04$ ), compared to salt-resistant (7%) adolescents. After the dietary intervention, all of the salt-sensitive adolescents in the high-potassium group achieved a dipper BP status with a drop in nocturnal diastolic BP and no change in daytime BP (daytime  $69 \pm 5$  vs.  $67 \pm 5$ ; nighttime  $69 \pm 5$  vs.  $57 \pm 6$  mmHg). These results suggest that a positive relation between dietary potassium intake and BP modulation can prevail, although daytime BP may be unchanged by a high-potassium diet.

Other investigations have also shown beneficial effects of increasing potassium on BP responses in salt-sensitive populations. For example, Fujita and Ando (1984) demonstrated that salt-sensitive hypertensive patients who were

given a potassium supplement (96 mmol/24 h) while on a high sodium diet showed significantly greater decreases in MBP after 3 days when compared to non-supplemented hypertensive patients. Svetkey et al. (1987) demonstrated a significant drop in both systolic and diastolic BP after 8 weeks of potassium supplementation (64 mmol/24 h vs. placebo) among mildly hypertensive patients. Similarly, a 2-year randomized intervention in China found that systolic and diastolic BP decreased on average by 5.9 and 2.8 mmHg, respectively, in an experimental group that used a potassium- and calcium-infused salt substitute. In a comparison group in which sodium intake was restricted, systolic and diastolic BP were reduced by 5.8 and 1.0 mmHg, respectively, indicating that use of the salt substitute was as effective at reducing BP as sodium restriction (Mu et al. 2009).

A number of reviews on the influence of potassium on BP responses have also shown positive inverse associations between high-potassium intake and BP responses in primarily adult populations (Whelton et al. 2002; Linas 1991; Cappuccio and MacGregor 1991). The mechanisms underlying BP non-dipping status are unknown. One potential mechanism by which potassium may alter nighttime BP may involve potassium-related natriuresis (Krishna et al. 1989; Weinberger et al. 1982). Restricting potassium intake has been associated with sodium retention; potassium supplementation results in natriuresis. Some investigators suggest that the effect of potassium on urinary sodium excretion, plasma volume, and mean arterial pressure could be evidence of a potassium-mediated vasodilatory effect on BP (Linas 1991). If non-dippers have excess SNS activity and increased peripheral resistance during sleep, this potassium-mediated vasodilatory effect could explain the reversal of non-dipping status as in a prior study (Wilson et al. 1999c). Other studies that support this hypothesis show that intrabrachial arterial infusions of potassium chloride increase forearm blood flow and decrease forearm vascular resistance in healthy adults (Fujita and Ito 1993; Phillips and Robinson 1984). Potassium supplementation given in combination with a high sodium diet also suppresses the increase in

catecholamine responses typically seen in response to salt loading (Campese et al. 1982). Previous studies have shown that total peripheral resistance and norepinephrine responses to stress are greater in offspring of hypertensives than in normotensives (Stamler et al. 1979). Several adult studies have also confirmed that SNS activation occurs in individuals with elevated nighttime BP (Kostic and Secen 1997). In summary, these data support the hypothesis that the SNS may be important in non-dipping BP status.

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## Nutrition and Dietary Adherence in Youth

Several lines of evidence suggest that targeting families may be important for promoting healthy dietary adherence in children and adolescents. Previous research has demonstrated moderate aggregation of dietary variables among adolescents and their parents (Patterson et al. 1988). Furthermore, because family members often share a genetic predisposition to health risk factors, family involvement may be important in motivating adolescents to improve their long-term eating habits. Parents and peers may serve as role models for adolescents by consuming foods that are healthy and by reinforcing dietary knowledge and behaviors learned in schools (Perry et al. 1988). Recent association studies have shown that heritable variants in genetic coding relate to blood pressure response to a low sodium family-based intervention. In such studies Chinese families were asked to adhere to either a low sodium diet, a high sodium diet, or a high sodium plus potassium supplementation diet, and the results were correlated with genetic variants. The responsiveness of family members' systolic and diastolic BPs to the low sodium diet was associated with variants in the reninase (RNLS), serum/glucocorticoid regulated kinase (SGK1), and adiponectin genes (Chu et al. 2015, 2016; Wang et al. 2014). A genome-wide association study showed that the compounding risk of eight heritable variants as associated with changes in BP responses to dietary sodium and potassium intervention, in a dose-response pattern (He et al.

2013). Similarly, genetic variants in the renin-angiotensin-aldosterone also were associated with a dose-response effect on individual BP responses of participants to dietary potassium intake (He et al. 2011). Together, these findings provide foundational evidence that dietary interventions likely interact with genetic predisposing factors to influence BP changes in response to alterations on sodium and potassium intake.

Social support from family members may also influence adherence to dietary interventions. Parents may encourage adolescents to adopt healthy dietary behaviors, which in turn may decrease the risk for cardiovascular disease and chronic illness. Wilson and Ampey-Thornhill (2001) examined the relationship between gender, dietary social support (emotional), and adherence to a low sodium diet. Healthy African-American adolescents ( $N = 184$ ) participated in an intensive 5-day low sodium diet (50 mEq/2 h) as part of an HTN prevention program. Girls who were compliant (urinary sodium excretion  $[U_{NaV}] < 50$  mEq/24 h) reported higher levels of dietary support from family members than boys who were compliant ( $U_{NaV} < 50$  mEq/24 h). In contrast, boys who were adherent reported lower levels of dietary support from family members than boys who were nonadherent.

In a study by Nader et al. (1989), Caucasian, African-American, and Mexican-American families were randomly assigned to a 3-month low sodium, low-fat dietary program or to a no-treatment group. The treatment group showed a greater increase in social support specific to diet than the no-treatment group. In summary, these studies provide evidence that familial support may be important for increasing adolescents' adherence to healthy dietary programs that could ultimately decrease the risk of HTN and cardiovascular complications.

Another way that parents, teachers, and peers may influence adolescents' adherence with healthy eating habits is through role modeling. Cohen et al. (1989) randomly assigned adolescents to either peer-led or parent-led promotions of a low sodium, low-fat dietary intervention. At the end of the intervention, both groups showed equal effectiveness in changing nutritional habits.



The peer-led intervention, however, was more effective in reducing BP.

Previous research also suggests that the incorporation of behavioral skills training and developmentally appropriate dietary interventions may be most effective in promoting long-term changes in sodium and/or potassium intake (e.g., increased fruit and vegetable intake). For example, in a study conducted by Gortmaker et al. (1999), 1,295 sixth- and seventh-grade students from public schools in Massachusetts participated in a school-based intervention over 2 years to reduce the prevalence of obesity. The intervention was based on social cognitive theory (SCT) and behavioral choice theory. Treatment sessions were incorporated into the existing curricula, used classroom teachers, and included the students increasing their fruit and vegetable intake. Schools across four study sites were randomized to either the SCT treatment that focused on behavioral skills or a control condition. After 3 years, these intervention schoolchildren exhibited significant changes in improved knowledge, intentions, self-efficacy, dietary behavior, and perceived social reinforcement for healthy food choices.

Some studies have provided insight into the importance of targeting eating patterns for improving food choices related to high-potassium/low sodium foods such as fruit and vegetable intake (Simons-Morton et al. 1990). In 943 third to fifth graders, fruit juices accounted for 6.1% of the total food selections for boys and 6.6% for girls. Vegetables accounted for 15.7% of total selection for boys and 16.2% for girls. Fruit was more likely consumed for snacks than for meals, and vegetables were eaten at the same rate for snacks, at lunch, and at supper. Consequently targeting an increase in fresh fruits and vegetables in all meals may be one effective approach to improving electrolyte intake in children.

Several studies have demonstrated sex differences in adherence to sodium restriction and dietary potassium supplementation. Sinaiko et al. (1993) reported urinary electrolyte excretion data over the course of a 3-year intervention in fifth through eighth graders. Boys were less likely to

comply with a sodium restriction of 70 mmol/day than girls. Subsequently, BP effects were only significant for girls. In a study by Wilson and Bayer (2002), boys were more likely than girls to comply with a 3-week dietary intervention of increasing potassium to 80 mmol/day intake. However, Krupp et al. (2015) assessed the impact that fruits and vegetables (FV) and sodium intake has on BP in 206 adolescent males ( $n = 108$ ) and females ( $n = 98$ ). The Krupp et al. (2015) study utilized participants in the Dortmund Nutritional and Anthropometric Longitudinally Designed study, which had data collected in adolescence (11–16 years) and early adulthood (18–25 years). Interestingly, results revealed sex differences with the impact that FV and sodium has on BP. Specifically, they found that in healthy adolescent girls, higher FV intake was predictive of lower systolic BP, where there was no difference in healthy boys. On the contrary, they found a significant reduction in systolic BP for adolescent boys who consumed less sodium, but there was no difference for adolescent females (Krupp et al. 2015). These studies suggest that boys, in particular, may be more likely to comply with high-potassium diets that emphasize adding foods to the diet, compared to low sodium diets that focus on eliminating foods from the diet. Their findings highlight the importance of understanding sex differences in promoting healthy diets for males and females with regard to blood pressure. Further research is needed to more fully explore the long-term effectiveness of dietary electrolyte interventions in boys versus girls and among youth in general.

Finally, researchers conducted a meta-analysis of studies assessing DASH diet adherence (Kwan et al. 2013). They found nine studies that met their search criteria, but there was no consensus on the best method of assessing adherence. The studies included had used an array of assessment methods, from more objective approaches (e.g., urinary excretion) to more subjective measures (e.g., dietary intake assessments). However, they did conclude that the development of effective approaches to measure compliance of the DASH diet should be the focus of future research (Kwan et al. 2013).

## Conclusions and Implications for Future Research

This chapter has provided data with evidence that promoting effective nutritional-electrolyte-focused interventions may be useful. Reducing sodium and increasing potassium intake are effective approaches for preventing cardiovascular risk in children and adolescent populations, and research suggests that adherence to high-potassium dietary interventions is higher than that for low sodium diets. The role of dietary intake on BP markers suggests that further attention should be paid to promoting positive dietary lifestyle skills in youth. However, other important factors must be considered, including those related to obesity and unhealthy lifestyles. Further, abnormal SNS activity may be linked to the factors that lead to elevated BP as reviewed in this chapter. Promoting healthy diets that target decreasing sodium and increasing potassium may help to decrease SNS activation. Finally, minority populations, and especially African-American youth, are at highest risk for developing HTN in early adulthood, and efforts should focus on preventing HTN in these communities. Continued efforts will be needed to address disparities in cardiovascular risk and obesity-related risk in underserved and minority youth.

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## Cross-References

- ▶ [Ambulatory Blood Pressure Monitoring Methodology and Norms in Children](#)
- ▶ [Cardiovascular Influences on Blood Pressure](#)
- ▶ [Development of Blood Pressure Norms and Definition of Hypertension in Children](#)
- ▶ [Ethnic Differences in Childhood Blood Pressure](#)

- ▶ [Insulin Resistance and Other Mechanisms of Obesity Hypertension](#)
- ▶ [Monogenic and Polygenic Contributions to Hypertension](#)
- ▶ [Obesity Hypertension: Clinical Aspects](#)
- ▶ [Stress and Salt Sensitivity in Childhood Hypertension](#)

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## Abstract

The endothelium is a critical mediator of blood pressure homeostasis through its roles in producing and interacting with circulating vasoactive compounds, most notably nitric oxide. Endothelial dysfunction is a marker of cardiovascular disease and may develop under a variety of conditions commonly observed in the pediatric population including chronic kidney disease, acute kidney injury, and childhood obesity. Ongoing endothelial dysfunction eventually leads to adaptive mechanisms, namely, vascular remodeling by which the structure of resistance vessels is altered, as is systemic blood pressure. Multiple factors central to the endothelium contribute to and perpetuate vascular remodeling including hemodynamic forces, reactive oxygen species, and the adipokine adiponectin.

## Keywords

Endothelium • Endothelial dysfunction • Vascular remodeling • Pediatric hypertension • Nitric oxide • Adiponectin • Reactive oxygen species

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## Introduction

While hypertension is a systemic disease involving many organ systems, there is new recognition that certain cell types, endothelial cells in particular, may contribute disproportionately to the pathophysiology of this condition. Endothelial cells are uniquely positioned as the first interface between the blood and the blood vessels and are important mediators of inflammation, proliferation and vascular reactivity. Indeed, endothelial health is both a marker of overall cardiovascular health and reflects the sum of ongoing beneficial

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and detrimental influences on the vasculature. This chapter reviews the ways in which the endothelium maintains vascular homeostasis, the conditions under which vascular homeostasis becomes deranged, and the ensuing vascular remodeling that occurs as a result of prolonged endothelial dysfunction.

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## Role of the Endothelium in Blood Pressure Homeostasis

The endothelium is a critical player in maintaining vascular homeostasis. Though vessel wall resistance has long been recognized as a key variable in blood pressure regulation and primary hypertension (Folkow 1982), more complete understanding of vessel wall biology has clearly identified interactions with the endothelium and circulating vasoactive substances, including nitric oxide (NO), angiotensin II (AII), and endothelin as equally important (Singh et al. 2010). Perhaps the most important of these is nitric oxide, produced in the endothelium by endothelial nitric oxide synthase (eNOS). eNOS is a calcium-dependent enzyme regulated by protein phosphorylation, protein-protein interactions, and its subcellular localization into perinuclear and plasma membranes (Fulton et al. 2001). NO is recognized to mediate many processes crucial to endothelial and blood vessel health including promotion of vessel wall relaxation and lowering of blood pressure.

The mechanism by which eNOS-derived NO modulates blood pressure is complex and is postulated to involve the kidney as well as the blood vessels. eNOS has been shown to be expressed not only in the vascular endothelium but also in certain epithelia in the nephron, including in the thick ascending loop of Henle (Wu et al. 1999). For example, NO has been shown to inhibit the Na-K-2Cl transporter in the thick ascending limb, thereby reducing renal sodium reabsorption in this nephron segment (Guarasci and Kline 1996; Herrera et al. 2006a). Multiple laboratories have demonstrated that increased salt intake in animal models is associated with increased NO in the kidney. This effect likely involves endothelin as

endothelin receptor antagonists have been shown to prevent this high-salt diet-induced increase in eNOS expression (Herrera and Garvin 2005; Herrera et al. 2006a, b; Mount and Power 2006).

In addition to its ability to limit sodium reabsorption, eNOS-derived NO has also been shown to lower blood pressure via several discrete signaling pathways. For example, Li et al. have demonstrated that use of a protein kinase C (PKC) inhibitor, midostaurin, in the spontaneously hypertensive rat model, can increase eNOS protein, mRNA, and NO bioavailability (Li et al. 2006). PKC inhibitors are currently being considered as potential antihypertensive agents in humans, but studies are still awaited (Khalil 2013; He et al. 2014). The Rho/Rho-associated kinase (ROCK) pathway has also received attention as a potential avenue of blood pressure regulation by means of NO. ROCK activation has been found to result in lower levels of eNOS mRNA in cultured cells (Noma et al. 2006; Takemoto et al. 2002), and eNOS-null mice have been shown to have higher levels of ROCK activity as compared to normal mice (Williams et al. 2006). Chronic ROCK activation has been associated with cardiovascular disease, including hypertension, in humans (Soga et al. 2011). However, it is not clear if ROCK activation increases cardiovascular risk or cumulative cardiovascular risk enhances ROCK activity (Soga et al. 2011).

Other vasoactive substances that are secreted by the endothelium and contribute greatly to vascular homeostasis are the endothelins. These are a three-member family of small peptides – endothelin -1, -2, and -3. Endothelin-1 (ET-1) is most important in the vasculature and is produced constitutively (Inoue et al. 1989). It is a powerful vasoconstrictor and can induce inflammatory responses, both key properties in maintaining vascular homeostasis. The molecular identity of this molecule was not elucidated until 1988 by Yanagisawa and colleagues (Yanagisawa et al. 1988) but there is much that is still poorly understood. In contrast to NO, which is generally regarded as a disease-inhibiting substance, ET-1 is one of the few endogenous substances, which, when perturbed, may be regarded as disease promoting by inducing cell proliferation,

inflammation, coagulation, and vasoconstriction (Barton and Yanagisawa 2008). ET-1 production is upregulated with age and during the development of aging and development of chronic disease, tipping the vascular milieu from protective to detrimental vascular milieu which may initiate and potentiate endothelial dysfunction.

More recently, C-type natriuretic peptide (CNP) has been recognized to be important in maintaining vascular homeostasis. Through elegant studies in a mouse knockout model, Moyes and colleagues demonstrated that endothelial-specific deletion of CNP resulted in vascular dysfunction, hypertension, and atherogenesis (Moyes et al. 2014). Those investigations further showed that CNP is a critical component of the non-prostanoid, non-NO vasorelaxation in resistance vessels as well as in preserving the integrity of the blood vessel wall.

In addition to its role as a generator of vasoactive substances, the endothelium also contains myriad receptors which allow it to respond to circulating molecules. One of the most relevant of these with respect to blood pressure homeostasis is the glucocorticoid receptor which binds its endogenous ligand, cortisol.

There is evidence that confirms the presence of the glucocorticoid receptor in the vascular endothelium (Imai et al. 1989; Piovesan et al. 1990), but little is known about its role there. In vitro experiments with endothelial cell culture models have suggested that glucocorticoids regulate vascular reactivity via suppression of the production of vasodilators such as prostacyclin and nitric oxide which would lead to vasoconstriction. However, Provencher et al. demonstrated an increase in angiotensin II receptor levels yet a decrease in endothelin-1 levels in response to synthetic glucocorticoids in a cell culture model of vascular smooth muscle cells (Provencher et al. 1995); those results would lead to vasodilation. Such contradictory results led the authors to speculate that glucocorticoids may function as modulators of vascular inflammation and not solely as vasoconstrictive agents.

Experiments performed to study the role of glucocorticoids and glucocorticoid receptors have compared intact vessels to injured vessels

in which the endothelium has been mechanically stripped and hence are devoid of all endothelial function. Wallerath et al. suggest that it is the ability of glucocorticoids to destabilize endothelial nitric oxide synthase (eNOS) mRNA and reduce eNOS protein expression that is responsible for the ensuing hypertension observed in rats treated with dexamethasone (Wallerath et al. 2004). More recent studies in isolated rat aortas showed that, through the glucocorticoid receptor, glucocorticoids could decrease expression of guanosine triphosphate cyclohydrolase 1 (GTPCH1) mRNA, the rate-limiting enzyme in the production of tetrahydrobiopterin (BH4), a cofactor for nitric oxide synthase (Mitchell et al. 2004). However, in that series of studies, eNOS mRNA levels were not significantly different in control vessels than in those treated with dexamethasone.

Using a mouse model (Goodwin et al. 2011), the glucocorticoid receptor, was ablated from the vascular endothelium by using Tie-1 Cre, which allows tissue-specific deletion of the receptor. Interestingly, these knockout animals had a small but statistically significant increase in their baseline blood pressure, the source of which could not be entirely explained. In addition, the knockout animals were almost completely resistant to glucocorticoid-induced hypertension and conspicuously lacked the pressure natriuresis observed in another model in which the vascular smooth muscle glucocorticoid receptor is ablated (Goodwin et al. 2008). Intravital microscopy studies done in real-time on resistance vessels from animals lacking the endothelial glucocorticoid receptor revealed a statistically significant decrease in vessel contractility to the glucocorticoid receptor-specific ligand dexamethasone when compared to wild-type animals (Goodwin et al. 2011). The contractility to phenylephrine was similar between the two groups (endothelial glucocorticoid receptor knockouts and wild types) suggesting that loss of the endothelial glucocorticoid receptor confers a specific contractile defect in these animals, presumably preventing them from mounting a hypertensive response to systemic dexamethasone. In that study whole-blood nitric oxide levels were not different between the two groups though the possibility of differences in

nitric oxide in local vascular beds could not be ruled out (Goodwin et al. 2011).

Other investigators have examined nitric oxide derangements with *ex vivo* studies in rats. In 2009, Aras-Lopez et al. evaluated electrical-field stimulation-induced neuronal nitric oxide release in mesenteric arteries of Wistar-Kyoto (WKY) rats, which are normotensive, and spontaneously hypertensive rats (SHRs) and the role of protein kinase C (PKC) in these responses (Aras-Lopez et al. 2009). Through a series of manipulations involving various PKC inhibitors, the authors demonstrated that dexamethasone was able to reduce neuronal nitric oxide release in arteries from SHRs but not WKY rats and that this effect was mediated through activation of glucocorticoid receptors. That study was novel in that it addressed the possibility that glucocorticoids exert their hypertensive effects, at least in part, by altering the neuronal nitric oxide release of the perivascular innervation of these tissues (Aras-Lopez et al. 2009). Thus, there may be differential effects of glucocorticoids on the various nitric oxide isoforms, which appear to be affected by the overall milieu.

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## **Etiologies of Endothelial Dysfunction and Resultant Blood Pressure Derangements**

Given the clear importance of the vascular endothelium in maintaining normal blood pressure, it is not surprising that endothelial dysfunction would aggravate or even precipitate hypertension. Let us next examine conditions under which endothelial dysfunction develops.

### **Chronic Kidney Disease**

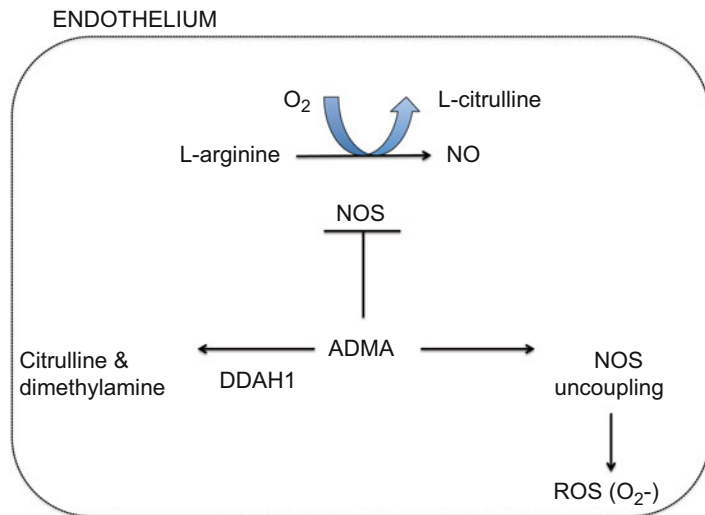
It is well known that the leading cause of death of patients on dialysis, both children and adults, is cardiovascular disease. Perhaps what is less well recognized is that patients with chronic kidney disease (CKD), not yet on dialysis, also have increased cardiovascular risk, in excess of what would be expected based on accepted risk factors (Go et al. 2004; Khandelwal et al. 2016). Emerging

data suggest that endothelial dysfunction makes a key contribution. Several functions of the endothelium have been shown to be defective in uremic states, including derangements in angiogenesis (Jacobi et al. 2006), vascular permeability (Harper and Bates 2003), and endothelial-dependent vasodilation (Verbeke et al. 2011). Deficits in NO bioactivity have also been reported in CKD (Baylis 2006), the reasons for which are not well understood but are an active area of investigation.

Asymmetric dimethylarginine (ADMA), a metabolite of arginine, is an endogenous inhibitor of nitric oxide synthases, and  $\iota$ -arginine can be metabolized to  $\iota$ -citrulline and NO by eNOS, its main substrate. Accordingly, provision of additional arginine, either as an acute or chronic manipulation, results in increased production of nitric oxide and improved endothelial function (Loscalzo 2004). It is known that ADMA is mainly absorbed by endothelial cells with extracellular levels being severalfold lower than intracellular levels. Thus, small changes in plasma ADMA are able to change intracellular ADMA and NO levels significantly (Cardounel et al. 2007). Accordingly, the arginine-NO pathway (Fig. 1) is of great interest in the study of endothelial dysfunction.

Increased ADMA levels in dialysis patients were first described over two decades ago (Vallance et al. 1992a, b). At present there are over one dozen studies that have clearly demonstrated a statistically significant increase in ADMA in patients with CKD compared to controls (Aldamiz-Echevarria and Andrade 2012). Interestingly this increase is also seen in renal transplant patients, who usually also suffer from varying degrees of endothelial dysfunction, increased levels of reactive oxygen species, and, clinically, hypertension (Zhang et al. 2009). Recent studies have demonstrated that concentrations of ADMA present in patients with kidney failure can decrease NO generation (Kielstein et al. 2004). Further it has also been shown that in a 5/6 nephrectomy rodent model, the enzyme dimethylarginine dimethylaminohydrolase (DDAH), the metabolizer of ADMA, is decreased, while the enzyme protein arginine methyltransferase (PRMT), the catalyzer of ADMA, is increased (Matsuguma et al. 2006). In addition to these enzyme

**Fig. 1** Arginine-nitric oxide metabolic pathway illustrating the inhibitory role of ADMA on NO generation. *NO* nitric oxide, *NOS* nitric oxide synthase, *ADMA* asymmetric dimethylarginine, *DDAH1* dimethylarginine dimethylaminohydrolase 1, *ROS* reactive oxygen species



imbalances, two additional mechanisms have been postulated to account for the increased ADMA levels found in CKD patients – an increased rate of protein turnover and impaired renal excretion of ADMA (Aldamiz-Echevarria and Andrade 2012).

Though the ADMA pathway has not been as well studied in children as in adults, there are some data in this population. Enzyme levels are typically higher in children as compared to adults, due to immaturity of the enzyme system. Increased arginine-to-ADMA ratios, an index for NO, were found to correlate positively with systolic BP, measured by ABPM, and left ventricular (LV) mass in children with early CKD stages 1–3 (Chien et al. 2015). ADMA levels have been shown to be upregulated in children with homocystinuria (Kanzelmeyer et al. 2012) and diabetes (Heilman et al. 2009), both conditions in which blood pressure elevation and endothelial dysfunction are common.

### Acute Kidney Injury

In addition to the smoldering endothelial injury, which may persist over years in patients with CKD, endothelial damage may also result from temporally brief but severe episodes of acute kidney injury (AKI). The hallmark of AKI is a reduction in glomerular filtration rate (GFR), resulting from a sustained increase in renal vascular resistance. Evidence from animal models of ischemia-

reperfusion injury supports the notion that endothelial damage contributes to the reduction in renal blood flow in that model system (Sutton et al. 2003). Endothelial dysfunction also has been shown to result in impaired vasodilator capacity, due to the impairment of eNOS function, demonstrated by loss of vasodilator responses to bradykinin and acetylcholine in a rodent model (Conger et al. 1988). Furthermore, as the one of the functions of eNOS in the kidney is to maintain medullary blood flow in response to vasoconstrictors such as angiotensin II (Zou et al. 1998), deranged eNOS function would predispose to hypertension. Surprisingly, it has been noted that renal autoregulation is compromised for up to 7 days following ischemic injury, well beyond the point at which renal blood flow has recovered to preinjury levels, suggesting that endothelial injury persists despite overall clinical recovery (Conger et al. 1994, 1995). Perhaps this observation contributes to the persistent hypertension that is noted in some patients following AKI episodes despite normalization of serum creatinine.

### Obesity

In this era of rampant childhood obesity in which nearly 20% of the adolescent population is classified as obese (Ogden et al. 2014), endothelial dysfunction is gaining attention as a surrogate marker

of cardiovascular disease, even in the pediatric population (see ► [Chap. 21, “Obesity Hypertension: Clinical Aspects”](#)). The effects of the interaction between hypertension and endothelial function on one another in the pediatric population are complex; furthermore puberty may affect the interaction (Bruyndonckx et al. 2016). Contrary to expectations, studies in obese prepubertal children have demonstrated greater functional reserve and greater adaptive capacity of the endothelium in response to stress as compared to responses in normal weight children (Radtke et al. 2013a). It has further been shown that HDL cholesterol, commonly regarded as a beneficial molecule with cardioprotective effects, is functionally impaired in obese children in that it is less capable of stimulating eNOS activity compared to its effect in normal weight children (Matsuo et al. 2013). The manipulation of HDL is an active area of investigation; HDL is now known to be a major carrier of microRNAs (miRs), small noncoding molecules that regulate expression of protein-coding genes. Early studies are currently underway in adult patients, though not yet in pediatric patients, to induce a more favorable miR profile via lifestyle modifications, including exercise, to prevent cardiovascular disease (Riedel et al. 2015).

The beneficial effects of physical activity on staving off or improving obesity are undeniable, but the relationship between physical activity and endothelial function is not as clear. In prepubertal children, exercise correlates strongly with endothelial function, as assessed by flow-mediated dilation of the brachial artery (Abbott et al. 2002), but this relationship is absent in adolescents (Radtke et al. 2013b). In young adults, the relationship is intuitive: healthy-weight adults stimulate endothelial function with physical activity, while obese individuals have a blunted response (Goran and Treuth 2001).

In addition to the very visible and physical limitations obesity imposes on general health and, as described above, on endothelial health, obesity may also be regarded as an endocrinopathy given the increased numbers and activity of adipocytes which are capable of secreting biologically active adipokines. At least two such adipokines, leptin and chemerin, have been found

to influence endothelial function. Leptin has been found to induce hypertension and endothelial dysfunction in female mice via an aldosterone-sensitive mechanism (Huby et al. 2016), and, in humans, circulating chemerin levels were correlated closely with endothelial function in obese youth in one study (Landgraf et al. 2012).

There are several other comorbidities that often segregate with obesity and may precipitate endothelial dysfunction. These include sleep apnea which is known to impair endothelial function (Li et al. 2013). In addition, insulin resistance may lead to endothelial dysfunction or vice versa. In a healthy state, insulin is a strong vasodilator, but in states of insulin resistance, endothelial cells are selectively resistant to this action, thus promoting a vicious cycle (Steinberg et al. 1994; Potenza et al. 2005). In a study of 248 normal children, psychological derangements, including anxiety, depression, and anger, have been reported to contribute to endothelial dysfunction, though the mechanisms are far from clear (Osika et al. 2011). As such problems are highly prevalent in obese children, we would speculate that another mechanism for endothelial dysfunction in the obese child may be through mood derangements.

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## Vascular Remodeling

Ongoing endothelial dysfunction ultimately results in adaptive mechanisms including vascular remodeling, characterized by alterations in the structure of resistance vessels. Vascular remodeling is an active and continuous process involving at least four different cellular processes including cell growth, cell death, cell migration, and extracellular matrix (ECM) synthesis and modification (Renna et al. 2013). Vascular remodeling may be physiological, as in the case of arteriogenesis or angiogenesis which occur during normal human development, or maladaptive, as may occur during vascular disease processes, such as atherosclerosis or hypertension. Vascular remodeling generally involves four cell types – fibroblasts in the adventitia, smooth muscle cells in the media, endothelial cell in the intima, and circulating macrophages (Fang and Yeh 2015).

## Hemodynamic Forces

Hemodynamic forces play a major role in endothelial cell health and plasticity. Shear stress, that is, flow parallel to the vessel wall, affects endothelial cell morphology. *In vivo*, there is evidence that cells exposed to steady, uniform flow are aligned with their long axis in the direction of flow and are elongated in shape. In contrast, cells exposed to disturbed flow are rounder and nonuniform in orientation (Langille and Adamson 1981). Shear stress is an important factor in regulating endothelial cell proliferation. Steady flow promotes reduced endothelial cell proliferation, while disturbed flow stimulates cell turnover and apoptosis (Davies et al. 1986). Cyclic strain/stretch, which occurs perpendicular to the blood vessel wall and is caused by the pumping of the heart inducing circumferential stress, also predisposes to endothelial migration (Von Offenbergsweeney et al. 2005); cyclic strain is necessarily increased in hypertension.

Endothelial cells respond to changes in hemodynamic forces by altering their production of vasoactive substances. Increases in shear stress generally favor vasodilation mediated by increase NO and eNOS, though multiple other vasoactive factors including prostaglandin and endothelin-1 are also affected (Hendrickson et al. 1999; Kuchan and Frangos 1993). Shear stress also affects expression of endothelial cell adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and selectins, which, in turn, may lead to leukocyte adhesion and platelet aggregation, both important events in the formation of atherosclerotic lesions and indicative of worsening vascular disease (Merten et al. 2000; Gerszten et al. 1998). Hemodynamic forces can also affect production of various endothelial cytokines and growth factors in addition to vasoactive substances. Imbalances in the expression of platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), transforming growth factor beta (TGF- $\beta$ ), interleukin-6 (IL-6), and interleukin-1 (IL-1) can create a domino effect, stimulating vascular smooth muscle cells to migrate and proliferate, creating a pro-inflammatory environment predisposed to progressive vascular disease (Cahill and Redmond 2016).

## Reactive Oxygen Species

Aberrant modulation of reactive oxygen species (ROS), through changes in cyclic and shear stress, as well as through generation of vasoactive substances, leads to endothelial dysfunction, which is associated with ongoing vascular injury and chronic changes. Endothelial cells and indeed all vascular cells have the ability to produce ROS, which are relatively unstable oxygen-centered-free-radicals. ROS are short-lived and difficult to measure directly.

It has been shown that in conditions of low shear stress, such as the disturbed flow that results from occlusive vascular disease or stenotic vessels, a signaling cascade is stimulated that results in NADPH oxidase (Nox) activation and ROS production (Chatterjee et al. 2012). Nox is activated by growth factors, cytokines, and vasoactive agents, all of which may be considered pro-hypertensive factors (Montezano et al. 2015b). Angiotensin II (Ang II) appears to be a particularly potent stimulator of Nox. Stimulation of both vascular endothelial and vascular smooth muscle cells with Ang II leads to increased Nox-induced ROS production which in turn activates redox signaling pathways (Raaz et al. 2014). Furthermore, Nox activation is increased in endothelial cells *in vitro* as well as in intact vessels in human hypertension (Konior et al. 2014; Montezano et al. 2015a). There are currently seven identified isoforms of Nox, all of which are expressed in the vasculature, but each with its own tissue distribution and cellular and subcellular localization (Montezano et al. 2015b).

The endothelial dysfunction associated with derangements in ROS signaling is mediated by changes in the redox state of ion channels, kinases, cyclases, activated protein kinases, phosphatases and proteins, and transcription factors. There exists a fine balance between the ROS/NO regulatory mechanisms. Steady flow seems to promote the activation of transcription factors important for vessel health including nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and Kruppel-like Factor 2 (KLF2), which, in turn, increase expression of superoxide dismutase (Takabe et al. 2011). Conversely, disrupted flow

favors upregulation of nuclear factor kappa-light-chain enhancer of activated B cells (NF- $\kappa$ B) and activator protein 1 (AP-1), which stimulate expression of disease-favoring proteins such as monocyte chemoattractant protein 1 (MCP-1) and intracellular adhesion molecule 1 (ICAM-1) (Hsieh et al. 2014). In redox-sensitive proteins, ROS signaling effects are mediated via changes in the specific cysteine residues. These posttranslational modifications may include S-nitrosylation, S-glutathionylation, sulfhydrylation, sulfenylation, disulfide bonds, and sulfinic and sulfonic acid (Choi et al. 2011) and result in changes to protein structure and function, which, in turn, cause a myriad of cellular effects, including vascular cell proliferation and/or apoptosis.

For example, under normal conditions, vascular smooth muscle cells demonstrate very low rates of proliferation. Under pathological conditions such as hypertension, increased levels of ROS influence redox-sensitive cell cycle processes via the aforementioned posttranslational modifications resulting in cell proliferation, dedifferentiation, and migration (Rao and Berk 1992). This proliferative phenotype then leads to the increased medial thickness, reduced lumen size, and increased stiffness that are the hallmarks of the detrimental vascular hypertrophy and remodeling observed in hypertension.

### **Renin-Angiotensin-Aldosterone System**

Another important contributor to the initiation and maintenance of vascular remodeling is the renin-angiotensin-aldosterone system (RAAS) (see ► Chap. 2, “Vasoactive Factors and Blood Pressure in Children”). Multiple lines of evidence clearly demonstrate that unchecked RAAS activation is deleterious. In vivo, infusion of Ang II in a rat model increases leukocyte adhesion in resistance vessels (Alvarez et al. 2004) and increases the expression of VCAM-1 in aorta via transcriptional activation of NF- $\kappa$ B (Tummala et al. 1999). Administration of losartan, an angiotensin receptor blocker, was found to abrogate the latter effects (Tummala et al. 1999). In studies using human

vascular smooth muscle cells (Kranzhofer et al. 1999), and peripheral blood monocytes (Hahn et al. 1994), Ang II induces expression of IL-6, MCP-1, and TNF $\alpha$ . Ang II can directly induce endothelial cell damage by inhibiting cellular regeneration; in addition, Ang II acts as a second messenger, activating the mitogen-activated protein kinase (MAPK) and protein kinase B (AKT) pathways, stimulating cell apoptosis, proliferation, and vascular dysfunction (Becher et al. 2011). Ang II is both pro-fibrotic and prooxidant (Qi et al. 2011). Ang II infusion has been further shown to induce production of ROS and activate Nox signaling and redox-sensitive genes (Rajagopalan et al. 1996). Consequently, the endothelium becomes more permeable (“leaky”) and allows migration of inflammatory cells into the blood vessel wall; the dysfunctional endothelium also recruits additional inflammatory cells and cytokines, compounding tissue injury and, ultimately, vascular disease (Pacurari et al. 2014).

As a corollary, RAAS blockade has clearly been found to improve vascular function and, in particular, endothelial dysfunction. Blockade with either an angiotensin receptor blocker (ARB) or an angiotensin converting enzyme inhibitor (ACEi) has been shown to improve NO bioavailability in humans (Mason 2011). Clinically, the reduction in cardiovascular events observed seems to exceed that expected from blood pressure lowering alone, suggesting that concurrent reduction in inflammation and oxidative stress directly improves endothelial dysfunction.

Aldosterone has also been shown to promote vascular remodeling. Though the effects of aldosterone on cardiac remodeling are well-established, there is recent recognition that aldosterone also contributes directly to vascular remodeling under conditions of endothelial dysfunction (Luther 2016). Adipocyte-derived growth factors have been shown to stimulate aldosterone secretion (Goodfriend et al. 1999; Ehrhart-Bornstein et al. 2003), and leptin itself is an aldosterone agonist (Ingelsson et al. 2007), perhaps explaining the strong association between obesity and hyperaldosteronism. Aldosterone directly stimulates adipocyte expansion (Urbanet et al. 2015) and decreases adiponectin evidence of expression

in vitro (Guo et al. 2008), which is directly correlated with endothelial dysfunction as well as insulin resistance (Wang and Scherer 2008).

In vivo studies have proved confusing in trying to assess the effects of aldosterone on endothelial cells. For example, obese mice that were fed a high-fat diet and isolated aortic rings from lean mice that received short-term aldosterone infusion, both of which were mineralocorticoid receptor (MR) replete, demonstrated impairment in NO-dependent vasodilation and endothelial dysfunction which could be reversed, in both models by genetic deletion of endothelial MR (Schafer et al. 2013). This study suggests that endothelial MR is involved in both the regulation of obesity-induced and aldosterone-induced endothelial dysfunction. Similarly, after a prolonged period of salt/deoxycorticosterone administration, endothelial cell-specific MR knockout mice were protected against cardiac ICAM-1 expression, macrophage infiltration, iNOS upregulation, and collagen deposition compared to controls despite the fact that there was not a significant change in blood pressure (Rickard et al. 2014). However, in a murine model, overexpression of the mineralocorticoid receptor in endothelial cells was protective when the mice were subjected to carotid artery injury and observed for thrombosis; this protection was mediated by increased vWF release and endothelial protein C receptor expression (Lagrange et al. 2014). The same investigators also demonstrated increased blood pressure and increased response to vasoconstrictors in this overexpression model (Nguyen Dinh Cat et al. 2010). The authors speculate that aldosterone activates the vascular endothelial MR, in the setting of healthy endothelium, which is anti-thrombotic, but in the setting of an injured or diseased endothelium, aldosterone, is pro-thrombotic.

## Adiponectin

Adiponectin is gaining recognition as a key mediator of endothelial dysfunction and cardiovascular. First discovered (Scherer et al. 1995) and cloned (Maeda et al. 1996) about two decades ago, adiponectin is a small protein hormone that is exclusively produced by adipose tissue and is comprised

of 244 amino acids. Adiponectin has effects in multiple tissues including liver, pancreas, and skeletal muscle; in endothelial cells, adiponectin activates the AMP kinase pathway which stimulates NOS production and bioavailability (Wang and Scherer 2008). Adiponectin production is decreased in all inflammatory processes. In humans, there is a strong negative correlation between blood pressure and plasma adiponectin levels (Kazumi et al. 2002; Baden et al. 2013), and adiponectin levels seem (Chow et al. 2007) to be an independent risk factor for the development of hypertension.

Evidence continues to mount that endothelial dysfunction may be the common link between hypoadiponectinemia and hypertension. Adiponectin is thought to regulate the enzymatic activity of eNOS via several mechanisms including increased mRNA stability, association with heat-shock protein 90 (Hsp90), a scaffolding molecule, and eNOS phosphorylation at Ser1179 (Fulton et al. 1999; Wang and Scherer 2008). In vitro, adiponectin treatment of cultured endothelial cells increases cyclooxygenase-2 (COX-2) expression and activates that Akt-dependent COX-2 signaling pathway (Rojas et al. 2014), which has been shown to protect the heart from ischemia-reperfusion injury in coronary artery disease (Szmitko et al. 2007). There are not many studies that have examined the ramifications of hypoadiponectinemia in children, as compared to adults. However, in the few studies that have been completed, adiponectin levels have been found to be statistically lower in obese children (Panagopoulou et al. 2008) and seem to be an independent risk factor for diabetes and cardiovascular disease (Bush et al. 2005; Cruz et al. 2004; Ogawa et al. 2005) – findings that would be anticipated, given data in adults. The question as to whether prenatal adiponectin levels determine postnatal levels and/or contribute to lifetime cardiovascular risk is unresolved and is an active area of investigation.

## MicroRNAs

In this age of increasing ease of genetic manipulation and broader understanding of the epigenetic



determinants of health, microRNAs have emerged as another contributor to vascular remodeling. MicroRNAs (miRs) are small, single-stranded, highly conserved, noncoding RNAs which can degrade mRNA or inhibit translation post-transcriptionally. Several miRs have been well described in endothelial cells and are thought to directly influence vascular remodeling. For example, miR-21 has been shown to regulate proliferation, migration, and tubulogenesis (Dentelli et al. 2010), purportedly through regulation of RhoB (Sabatel et al. 2011). miR-126 is also highly expressed in endothelial cells and is known to regulate angiogenesis during embryonic development (Fish et al. 2008) but has also been shown to have anti-inflammatory (van Solingen et al. 2011) and anti-atherogenic roles (Zernecke et al. 2009). miR-155, also found in endothelial cells, can be activated by increases in shear stress, such as may be found in the early stages of vascular remodeling, and in turn inhibits vascular inflammation by down regulation of the gene ETS-1, a transcriptional activator of inflammation (Fang and Yeh 2015). Also of note is miR-221/222, which is highly expressed in both vascular smooth muscle cells and vascular endothelial cells, but has differing functions which are dependent on cell type. While this miR aggravates neointimal hyperplasia in smooth muscle cells (Liu et al. 2009), it has been shown to be anti-inflammatory, anti-atherogenic, and anti-angiogenic in endothelial cells (Zhu et al. 2011; Poliseno et al. 2006). miRs are emerging as a new therapeutic strategy for treatment of cardiovascular diseases related to vascular remodeling.

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## Conclusions

Endothelial dysfunction is now recognized as a major risk factor for the development and perpetuation of hypertension in all age groups. Notably, some of the conditions presently increasing among children, including obesity and chronic kidney disease, may lead to endothelial dysfunction. Ongoing research efforts and clinical trials continue to uncover novel players in the complex regulatory systems and signaling pathways that direct the functions and fate of endothelial cells

often tipping the balance from the healthy vasculo-protective endothelium to a dysfunctional, disease-promoting endothelium which fuels many cardiovascular diseases. Unchecked endothelial dysfunction leads to maladaptive mechanisms including vascular remodeling, a complex interplay of proliferative, and largely pro-inflammatory changes occurring in multiple cell types, which may permanently alter vasculature and systemic blood pressure.

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## Cross-References

- ▶ [Cardiovascular Influences on Blood Pressure](#)
- ▶ [Cohort Studies, Meta-analyses, and Clinical Trials in Childhood Hypertension](#)
- ▶ [Epidemiology of Cardiovascular Disease in Children](#)
- ▶ [Hypertension in Chronic Kidney Disease](#)
- ▶ [Hypertension in End-Stage Renal Disease: Dialysis](#)
- ▶ [Hypertension in End-Stage Renal Disease: Transplantation](#)
- ▶ [Insulin Resistance and Other Mechanisms of Obesity Hypertension](#)
- ▶ [Obesity Hypertension: Clinical Aspects](#)
- ▶ [Obstructive Sleep Apnea and Hypertension](#)

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## Abstract

The pressure response to sodium is heterogeneous among both persons with normal blood pressure and with hypertension. Nevertheless, sodium restriction is typically recommended for everyone with hypertension. As reviewed here, categorizing a person as “salt sensitive” has important prognostic and therapeutic implications. Determination of salt sensitivity is typically accomplished by assessment of the pressure response to administration of an oral or intravenous sodium load. In this chapter, we discuss an alternative way to administer a sodium load through stress exposure. Animal and human studies have demonstrated clinically significant sodium retention during and after stress, which in effect generates positive sodium balance and thus delivers a sodium load. Persons demonstrating this response develop a volume-dependent blood pressure elevation. Similar to findings in salt-sensitive

populations, target organ changes have also been associated with impaired sodium handling during stress. Sodium retention in response to stress has been reported as improved or reversed after treatment with anti-hypertensive medications that block the renin-angiotensin-aldosterone system. Evidence suggests that the variability of the pressure response to dietary sodium intake and to stress should be considered in our strategies to prevent and control hypertension.

## Keywords

Salt sensitivity • Sodium • Stress-induced sodium retention • Pressure natriuresis • Sympathetic nervous system • Renin-angiotensin-aldosterone system • Obesity • Angiotensin II

## Abbreviations

ABPM	Ambulatory blood pressure monitoring
ACEi	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin receptor blocker
BMI	Body mass index
BP	Blood pressure
DASH	Dietary Approaches to Stop Hypertension
GFR	Glomerular filtration rate
GRK4	G protein-coupled receptor kinase 4
OR	Odds ratio

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RAAS	Renin-angiotensin-aldosterone system
SNS	Sympathetic nervous system

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## Introduction

Although there is a direct relation between sodium intake and blood pressure level in population studies, “sodium sensitivity” is heterogeneous within populations. Typically sodium sensitivity is defined as an elevation of blood pressure with administration of exogenous sodium and, in comparison, a drop in pressure with volume depletion or decreased sodium intake. Less well appreciated is the fact that variations in sodium handling during stress can also demonstrate salt sensitivity. In some persons, exposure to stress leads to sodium retention and blood pressure elevation. In studies of stress-related sodium retention, renal tubular responses control the endogenous response. Indeed, studies of the effects of stress on sodium handling in salt-sensitive people may offer insight into how environmental factors influence the development of hypertension.

## Sodium Intake and Blood Pressure

A positive association between sodium intake and blood pressure (BP) levels has been demonstrated in many animal and human studies (He and MacGregor 2006, 2009; Van Vliet and Montani 2008; Denton et al. 1995; Intersalt Cooperative Research Group 1988). A key animal study compared BP in 12 chimpanzees fed a diet that progressively increased its sodium content over several weeks to ten chimps fed their regular, low-sodium diet (Denton et al. 1995). Animals fed the high-salt diet had increasing BP that returned to baseline when the sodium intake returned to normal (Denton et al. 1995). Human population studies have shown that people fed a higher-salt diet have higher BPs than those consuming a modest salt intake (He and MacGregor 2009). The INTERSALT cross-sectional study conducted in the 1980s in 10,000 adults in 32 countries (Intersalt Cooperative Research Group 1988) confirmed this point. The influence of sodium intake on BP was recently verified in an even larger international study of >100,000 adults in 18 countries and with varying income levels (The PURE study) (Mente et al. 2014). In that study, BP increased by 2.11 mmHg systolic and 0.78 mmHg diastolic for each 1 gm increase in sodium intake. The findings in the PURE study correlated with age, the presence of hypertension, and sodium intake (Mente et al. 2014).

Similarly, in children a direct relation between salt intake and BP was appreciated by He et al., who evaluated cross-sectional data on 1,658 children and adolescents, ages 4–18 years, from the National Diet and Nutrition survey conducted in 1997 in the United Kingdom (He et al. 2008). In these free-living children, an increase in salt intake of 1 g (400 mg sodium) per day was associated with an increase in systolic BP and pulse pressure by 0.4 and 0.6 mmHg, respectively. Examination of NHANES (2003–2008) data from the United States also confirmed a positive association between BP and sodium intake (Yang et al. 2012). Analysis of those data on 6,235 US children and adolescents ages 8–18 years demonstrated a



progressive rise in systolic BP with increasing sodium intake quartile with accentuation of this association in overweight/obese participants. When children and adolescents in the highest sodium intake quartile were compared to those in the lowest quartile, the odds ratio (OR) for high BP was 1.98 for the overall group but was 3.51 for overweight/obese participants. These results were extended by Rosner et al. who examined additional NHANES surveys to expand the sample size to 11,636 and assessed BP based on values for normal weight children (Rosner et al. 2013). Even after adjusting for obesity, these investigators found an increased risk for elevated BP (prehypertension or hypertension) in children consuming more than 1.5 times the recommended dietary intake for sodium (OR 1.36). This effect was independent of race, age, and gender. While casual BPs have primarily been utilized to assess the relationship between sodium intake and BP, a recent small study conducted in Portuguese children ages 8–9 years utilized ambulatory blood pressure monitoring (ABPM). The investigators found that for each gram of salt intake, daytime systolic pressure increased by 1.00 mmHg in overweight/obese boys only. These results may have been influenced by a greater salt intake in males or possibly earlier onset of puberty in the females (Correia-Costa et al. 2016). Lastly, a relation between sodium and BP in children has also been implied by many studies that have analyzed the ability of salt restriction to reduce BP. He and MacGregor performed a meta-analysis of ten controlled pediatric trials involving 966 participants, ages 8–16 years (He and MacGregor 2006). As the methods used to assess adherence to salt restriction differed between trials, the authors calculated the percent reduction in salt intake for the individual study for analysis. Using this approach, the median reduction in salt intake was 42% with an interquartile range of 7–58%. Pooled results showed significant decreases of  $-1.17$  mmHg for systolic and  $-1.28$  mmHg for diastolic pressures, though seemingly small such changes in blood pressure would be amplified if achieved population wide (He and MacGregor 2006).

## Salt-Sensitive Populations

While the studies noted above support a relation between sodium and BP in unselected populations, this tendency is not universal but rather follows a Gaussian curve. This phenomenon was demonstrated by Weinberger et al., who evaluated the BP response to salt loading followed by volume depletion in 378 normotensive and 198 hypertensive persons (Weinberger et al. 1986). Participants were “loaded” with salt by infusion of 2 liters of 0.9% normal saline intravenously over 2 h and also received a high-salt diet during that time. The following day, volume depletion was induced by restricting dietary sodium intake to 10 mEq in conjunction with 40 mg of intravenous furosemide every 6 h for three doses. Salt sensitivity was defined by  $\geq 10$  mmHg difference in BPs obtained at completion of salt loading and at the end of volume depletion. Those participants demonstrating  $\leq 5$  mmHg change in pressure between the two periods (loading versus depletion) were considered salt resistant. Twenty-six percent and 51% of normotensive and hypertensive subjects, respectively, were classified as salt sensitive. A Gaussian distribution of BP response to salt loading and depletion was demonstrated for both hypertensive and normotensive subjects. Similarly, these authors demonstrated a normal distribution of salt sensitivity in normotensive adults fed a modestly salt-restricted diet ( $< 80$  mEq of sodium/day) for 3 months (Luft and Weinberger 1997). For both normotensive and hypertensive groups, salt-sensitive participants were more likely to be older than those who were salt resistant (Luft and Weinberger 1997; Weinberger et al. 1986).

Although older age is associated with salt sensitivity, an enhanced BP response to salt intake has been demonstrated in adolescents and young adults. In young adults, ages 18–23 years, Faulkner and Kushner demonstrated salt sensitivity by oral administration of 10 g of sodium chloride daily for 14 days (Falkner and Kushner 1990). Defining salt sensitivity as a  $> 5\%$  rise in mean

arterial pressure, 31% were identified as salt sensitive overall, (41% of normotensives and 23% of hypertensives). These results contrast with those of Weinberger et al. above which the frequency of salt sensitivity in hypertensive subjects was twice that of normotensives (Weinberger et al. 1986). Apart from dissimilarities in definitions of salt sensitivity and protocols, these conflicting results may also be related to the aging phenomenon and differences in racial composition of the study populations. Blacks represented 69% of the cohort studied by Falkner and Kushner as compared to 22% of those evaluated by Weinberger et al. Long-term studies in young adults by Falkner and associates demonstrated an association between the BP response to oral sodium loading and change in BP over 5 years (Falkner et al. 1992). Further studies in pediatric and young adult populations have suggested that obesity, hyperinsulinemia, African-American race, family history of hypertension, and low birth weight are risk factors for salt sensitivity (Falkner and Kushner 1990; Falkner et al. 1981, 1992; Simonetti et al. 2008; de Boer et al. 2008; Rocchini et al. 1989).

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### Mechanisms Generating Salt Sensitivity

Several different mechanisms can result in the phenotype of salt sensitivity. Less sodium is filtered when there is a decrease in glomerular filtration rate (GFR), which contributes to hypertension in persons with chronic kidney disease. However, this mechanism is not a likely factor for most people with essential hypertension, as GFR is typically normal or near normal. Impaired sodium handling by the renal tubule has been frequently invoked in the pathogenesis of salt sensitivity, but the specific segment(s) and abnormality(ies) enhancing reabsorption of sodium have yet to be established. Investigation of monogenic disorders such as Liddle's syndrome, apparent mineralocorticoid excess, and pseudohypoaldosteronism type II (see ► [Chap. 7, "Monogenic and Polygenic Contributions to Hypertension"](#)) has led to an appreciation that

defects in the functioning of the epithelial sodium channel heighted response to mineralocorticoids in the distal tubule or alteration in activity of WNK proteins increase BP (Fujita 2014). Although monogenic conditions are rare, subtle abnormalities in distal tubule sodium reabsorption may prove to be involved in the pathogenesis of essential hypertension. Additionally, sodium handling in the proximal tubule, a site of action for angiotensin II and the sympathetic nervous system (SNS), may play a role in determining BP levels (Burnier et al. 2006). Using lithium excretion as a marker, Chiolero et al. were able to link failure to reduce proximal tubule sodium reabsorption in response to a high sodium intake with salt sensitivity in animals and humans (Chiolero et al. 2001). Extensive research into the role of various natriuretic and anti-natriuretic systems and possible gene or gene products involved in generating the phenotype of salt sensitivity have been conducted (Elijovich et al. 2016). Whatever the route to the phenotype, salt sensitivity is complex and likely dependent, in most cases, on the interaction of genetic factors, the environment, and physiological conditions.

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### Is Clinical Determination of Salt Sensitivity Important?

Classification of patients with hypertension as salt sensitive identifies them as being at greater risk for hypertensive target organ changes and cardiovascular morbidity as compared to salt-resistant patients. For example, Bihorac et al. found increased frequency of hypertensive retinopathy, left ventricular hypertrophy, microalbuminuria, and higher serum creatinine in salt-sensitive hypertensive patients as compared to salt-resistant hypertensives (Bihorac et al. 2000). A greater risk for cardiovascular events has also been linked with salt sensitivity (Morimoto et al. 1997). Furthermore, studies support the contention that long-term survival among persons with hypertension is influenced by salt sensitivity. Weinberger analyzed long-term data on normotensive and hypertensive adults who had been previously classified as salt sensitive or salt resistant

(Weinberger et al. 2001). Salt-sensitive hypertensives had the poorest survival of all groups. Interestingly, persons who were normotensive but had been found to be salt sensitive demonstrated similar survival to hypertensives over time and had significantly reduced survival compared to normotensive salt-resistant adults. Identification of salt sensitivity may also be helpful in determining those patients for whom strict reduction in salt intake might not be advantageous (Mente et al. 2014; Kotchen et al. 2013). It has been suggested that sodium restriction may be detrimental in some populations such as patients with diabetes mellitus and patients with congestive heart failure on high-dose diuretics (Kotchen et al. 2013). Additionally investigators have raised concerns regarding long-term implications for salt-sensitive people who may have untoward metabolic and hormonal effects such as a reduction in insulin sensitivity and stimulation of the renin-angiotensin-aldosterone system (RAAS) (Kotchen et al. 2013; Graudal et al. 1998).

Additionally, pragmatically, the response to antihypertensive medications can be influenced by salt sensitivity. Weir et al. demonstrated that variation in salt intake influenced the response to an angiotensin-converting enzyme inhibitor (ACEi) versus a calcium channel blocker (Weir et al. 1998). Similar findings have been noted with other medications and non-pharmacologic interventions such as the Dietary Approaches to Stop Hypertension (DASH) diet and weight loss protocols (Sacks et al. 2001; Weir et al. 2001, 2010; Hoffmann et al. 2008). For example, the DASH diet was most effective in lowering BP when sodium intake was also restricted (Sacks et al. 2001). Thus, failure to consider salt sensitivity may compromise management of patients and may complicate trials of antihypertensive medications whose efficacy may differ based on the presence or absence of salt sensitivity among study participants.

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## Identification of Salt Sensitivity

The heterogeneity of the response to sodium loading indicates a difference in sodium handling in salt-sensitive versus salt-resistant persons. At a

given BP level, salt-sensitive persons demonstrate reduced sodium excretion compared to those who are salt resistant. For example, in a study of young adults, Falkner and Kushner (1990) observed a negative correlation between sodium excretion and change in mean BP after oral sodium loading in salt-sensitive participants ( $r = -0.28$ ,  $p < 0.01$ ). Similar findings have been reported by other investigators (Weinberger et al. 1986; Palacios et al. 2004; Rydstedt et al. 1986).

The complexity of protocols that assess salt sensitivity, as described above, and the resultant burden to patients have limited the clinical utility of establishing salt sensitivity (Nichols et al. 2012; Mattes and Falkner 1999). Thus, identification of salt sensitivity is most typically accomplished by demonstrating an increase in BP in response to sodium loading by either the enteral or parenteral routes. Novel approaches for the determination of salt sensitivity are under investigation. In a small study, Gidea et al. found that markers reflective of dopamine and/or angiotensin II activation can be identified in proximal renal tubule cells shed into the urine of patients previously identified as salt sensitive (Gidea et al. 2013). Additionally, analysis of ABPM to characterize an ABPM phenotype that predicts salt sensitivity has been promising (Castiglioni et al. 2013; Bursztyrn and Ben-Dov 2013). Castiglioni et al. found that the combination of reduced nocturnal dipping and increased pulse pressure identified salt sensitivity in untreated hypertensive patients with a sensitivity of 74% and specificity of 78% (Castiglioni et al. 2013). However, other investigators have not demonstrated reproducibility (Elijovich et al. 2016); thus, further validation would be required.

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## Stress and the Demonstration of Salt Sensitivity

The tactics for determination of salt sensitivity mentioned above are based on the ability of sodium loading or volume/sodium restriction to elicit clinically significant changes in BP. A potential alternative method to demonstrate salt sensitivity involves taking advantage of the antinatriuretic response to sympathetic nervous

system (SNS) arousal to identify people who retain rather than excrete sodium during stress, referred to as stress-induced sodium retention or impaired stress-induced pressure natriuresis (Harshfield et al. 2009). The stress-induced sodium retention phenomenon is manifested by one in five Caucasians and one in three African-Americans who retain sodium in response to stress. This response adds a volume component to the resistance-mediated increase in blood pressure during stress, which remains elevated until the volume expansion diminishes and thereby increases the sodium-induced blood pressure load through the kidneys. To study this phenomenon, an increase in BP is induced by exposure to stress tasks, such as a 10 min social stressor interview, a 10 min virtual reality car driving test, or a 10 min competitive video game.

The primary evidence for using a stress-response approach to classifying salt sensitivity comes from two convergent lines of research in the animal literature. One is the investigation by psychologists of the mechanisms through which stress contributes to hypertension via its effects on renal sodium handling. These include the pioneering studies by Friedman (Friedman and Iwai 1976) using a chronic conflict avoidance task in Dahl hypertensive rats and the extensive studies by Koepke (see recent review by Harshfield et al. 2009). The other is the work of the renal physiologist DiBona (1992, 2002, 2003), which defined the mechanisms through which SNS activation of the renal nerves can contribute to the development of hypertension in at-risk animals. Further studies by additional investigators implicate anti-natriuretic actions of stress-induced efferent renal sympathetic activity in the development of hypertension directly and indirectly by SNS stimulation of renin activity with subsequent increase in angiotensin II levels (Veelken et al. 1996; Le Fevre et al. 2003; Wagner et al. 1999). Generation of angiotensin II is presumed due to the observed effects of anti-renin-angiotensin system medications in blocking the stress-induced response pattern (Veelken et al. 1996; Le Fevre et al. 2003; Wagner et al. 1999).

## Factors Related to Stress-Induced Sodium Retention in Humans

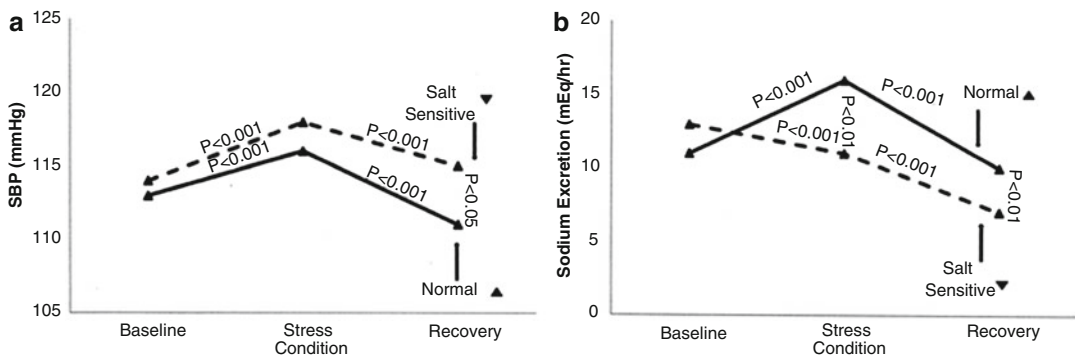
Surprisingly there have been very few human studies that examined changes in sodium excretion during mental stress. However, we and others have demonstrated stress-induced sodium retention and identified several factors associated with this phenomenon in humans (summarized in Table 1). The initial study by Light in 1983 in young adult Caucasian men reported that sodium retention during mental stress occurred more commonly in those with borderline hypertension or a parental history of hypertension (defined as high risk) as compared to those with a negative family history and normal BP (Light et al. 1983). In a subsequent study, Light and Turner reported that sodium retention was associated with higher cardiac output and stroke volume during stress as compared to sodium excretion during stress (Light and Turner 1992). Reduced natriuresis with stress was noted in blacks and in those with a family history of hypertension. Our group replicated these findings in studies on healthy normotensive African-American adolescents (Harshfield et al. 2002a, b, 2007). After consuming a controlled sodium diet for 3 days prior to testing, African-American youth (ages 15–18 years) underwent a 5 h protocol that included 1 h of stress (Harshfield et al. 2002b). Thirty-two percent of the participants demonstrated impaired pressure natriuresis with sodium retention, leading to a volume-mediated rise in BP (Harshfield et al. 2002b). The other participants had a resistance-mediated rise in their pressure that resulted in natriuresis and a return of the BP to normal (see Fig. 1).

It is well recognized that obesity is present in epidemic proportions in children and adolescents. A series of studies has examined the impact of greater adiposity on sodium retention during stress. Barbeau et al. compared sodium handling during stress in lean versus overweight/obese black youth (Barbeau et al. 2003). The overweight/obese group displayed a significantly smaller stress-related increase in sodium excretion, despite a similar

**Table 1** Studies demonstrating sodium retention during mental stress in humans

Authors	Participants	Diet	Stressor	Duration	Results
Light et al. (1983)	White males, borderline HTN or FH <sup>+</sup>	High Na <sup>+</sup> /fluid load	Competitive video games	60 min	Seminal study in humans showing sodium retention in high-risk subjects
Light and Turner (1992)	28 males: 14 black and 14 white	High Na <sup>+</sup> /fluid load	Competitive video games	60 min	First study to show race differences with sodium retention in
Harshfield et al. (2002a)	121 normals w/FH <sup>+</sup> , 14–27 years old	Ad lib	Combined tasks	180 min	First study to show a role for RAAS with 27% of participants showing sodium retention
Harshfield et al. (2002b)	118 black, 15–18 years old	3 days, Na <sup>+</sup> controlled	Competitive video games	60 min	34% sodium retention
Harshfield et al. (2003)	292 black and white aged 15–18	3 days, Na <sup>+</sup> controlled	Competitive video games	60 min	Body mass index related to sodium retention in males
Barbeau et al. (2003)	84 normal black 15–18 years old	3 days Na <sup>+</sup> controlled	Competitive video games	60 min	Percent body fat related to sodium retention
Wilson et al. (2004)	127 black and white, 15–18	3 days Na <sup>+</sup> controlled	Competitive video games	60 min	Percent body fat and Ang II related to Na <sup>+</sup> retention
Harshfield et al. (2007)	84 black and 105 white, 15–18 years old	3 days Na <sup>+</sup> controlled	Competitive video games	60 min	Greater sodium retention in blacks vs. whites
Jackson et al. (2001)	51 normotensive young adults	Ad lib	Combined tasks	180 min	ET-1 is associated with sodium retention
Mathur et al. (2015)	776 normotensive youth, 15–19 years old	3 days, Na <sup>+</sup> controlled	Competitive video games	60 min	ET-1 is associated with sodium retention

Adapted and used with permission from Harshfield et al. (2009) HTN hypertension, Ang II angiotensin II, FH family history



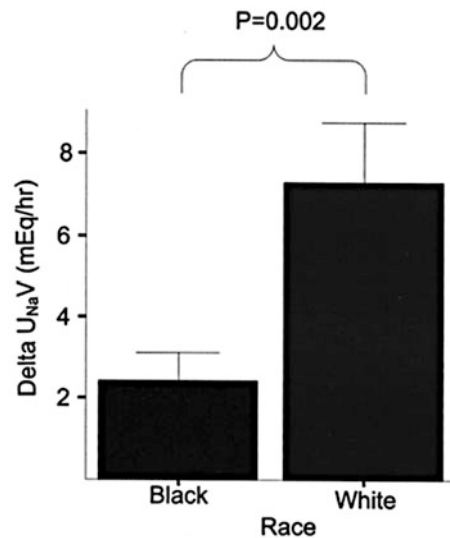
**Fig. 1** Stress-induced changes in systolic blood pressure and sodium excretion. Stress-induced changes in systolic blood pressure (SBP) shown in panel (a) and sodium excretion (mEq/h) shown in panel (b), based on direction of the stress-induced changes in sodium

excretion. Data expressed as least square means. Data compared for baseline, stress condition, and recovery periods (Adapted and used with permission Harshfield et al. (2002b))

increase in BP. A subsequent study by Wilson et al. was performed on a cohort of 127 youths that included both black and white participants (Wilson et al. 2004). Percent body fat independently accounted for 4.6% of the variance of the stress-induced change in sodium excretion and 11.2% of the variance of the level of sodium excretion during stress. Another study of 151 boys and 141 girls reported that body mass index (BMI) was inversely related to sodium excretion during the stress period in boys (Harshfield et al. 2003). The magnitude of the correlation became greater when data from boys with a BMI  $>25$  kg/m<sup>2</sup> were analyzed.

The propensity for salt sensitivity in African-Americans and older persons has been well recognized. In concordance with racial differences noted in conventional sodium loading studies, Light and Turner reported that sodium retention during stress occurred more frequently in black adults compared to white adults (Light et al. 1983). Similarly in adolescents, Harshfield et al. found that sodium excretion in response to stress was significantly lower in blacks compared to whites; see Fig. 2 (Harshfield et al. 2002a). The stress-induced increase in urinary sodium excretion was only  $2 \pm 6$  mEq/h in African-American adolescents compared to  $7 \pm 10$  mEq/h in white adolescents. With regard to the effect of age, recent data from our group has demonstrated that the magnitude of stress-induced sodium retention increases with age (GA Harshfield, CD Hanevold, unpublished, Augusta University and University of Washington).

Sodium retention during stress has been linked to preclinical measures of target organ damage (Harshfield et al. 2009). Specifically, African-American adolescents who retained sodium during stress have a 10% greater albumin excretion rate than those that excrete sodium during stress (Hanevold et al. 2008). Furthermore, sodium retention was associated with cardiac remodeling (Harshfield et al. 2002a), degradation of endothelial function (Maya et al. 2006), and diastolic dysfunction (Kapuku et al. 2003).



**Fig. 2 Racial differences in sodium excretion with stress exposure.** Bars signify change in sodium excretion (Delta U<sub>Na</sub>V) expressed in mEq/h before and after stress with standard deviations (Figure generated from data in Harshfield et al. 2002a)

### Mechanisms Generating Stress-Induced Sodium Retention

The mechanisms underlying stress-induced salt sensitivity in humans have yet to be established. Studies in animals have supported the importance of the RAAS and the SNS in the genesis of impaired sodium handling during stress. Working with Dahl rats, Koepke et al. demonstrated urine sodium retention when sodium loading was followed by behavioral stress (Koepke et al. 1983). Administration of propranolol followed by the same procedure resulted in a higher sodium excretion. Treatment with other beta-blockers characterized by less central nervous system penetration under the same protocol showed impaired sodium excretion. Of note, Light et al. were not able to replicate this effect of beta-blockers in humans (Light 1992). A role for the SNS was also supported by work in Sprague-Dawley rats subjected to air stress (Veelken et al. 1996). In these studies, anti-natriuresis was shown to be

associated with renal sympathetic nerve activity and was abolished by renal denervation or by pretreatment with an angiotensin receptor blocker (ARB). A recent study also highlighted the role of RAAS system and the importance of angiotensin II in generating salt sensitive increases BP in response to stress (Loria et al. 2015). Independent from angiotensin II, in this Dahl rat model, salt sensitivity did not significantly impact BP patterns in response to stress.

Drawing on the above animal studies, mechanistic studies in humans have focused on the role of the RAAS (as summarized in Table 2). Treatment for a month with an ACEi improved sodium excretion in Caucasian hypertensive adults as compared to those treated with placebo (Fauvel et al. 1994). Similarly, other investigators have demonstrated that treatment with an ACEi lessened sodium retention (Schneider et al. 2001; Rollnik et al. 1995) in Caucasian adults. We recently expanded these findings to treatment with an ARB in a normotensive African-American population (GA Harshfield, CD Hanevold, DL Stewart, LA Ortiz, V George, SK Mathur, unpublished data, Augusta University and University of Washington). The study demonstrated a change from sodium retention to sodium excretion during stress with pretreatment with an ARB. The BP response to stress was also reduced.

Data on stress-induced sodium retention in people with a family history of hypertension have been conflicting. Two studies reported that stress-induced sodium retention was greater in

persons with a positive family history (Light et al. 1983; Harshfield et al. 2002a), while two studies did not find differences between persons with or without a family history of hypertension (Ducher et al. 2002; Schneider et al. 2001). Subsequent investigation in twins suggested racial differences in heritability for sodium excretion during stress, which was greater in blacks (58%) than in whites (42%) (Harshfield et al. 2009). Furthermore, these heritabilities could be attributed to genes that were only expressed under stress. The stress-specific genetic influences were twice as large in blacks (47%) as compared to whites (23%). Approximately 40% of the individual differences in the sodium excretion in response to stress could be explained by genetic factors in both blacks and whites. Additionally, a subsequent genetic study identified the potential significance of the G protein-coupled receptor kinase 4 (GRK4) in sodium handling and hypertension (Zhu et al. 2006). Overall, these studies suggest a role for a genetic contribution to sodium retention. However, the specific genes involved in this complex response pattern (or trait) remain to be established.

## Conclusions

Identification of salt sensitivity carries important therapeutic and prognostic implications. Unfortunately, definitions and methodologies utilized to characterize salt sensitivity have varied between studies making comparisons of the findings

**Table 2** Studies supporting that RAAS blockade decreases sodium retention during stress in humans

Study	Participants	Diet	Stressor	Duration	Results
Fauvel et al. (1994)	10 HTN on ACEi 10 placebo	Ad lib	Mental stress	60 min	ACEi improved
Rollnik et al. (1995)	21 HTN, 27 normal adult white males	5 days, 10 mEq Na <sup>+</sup> , hospitalized	Mental stress, with monetary incentive	60 min	ACEi improved
Schneider et al. (2001)	66 normals (33 FH <sup>+</sup> ), 36 mild HTN, 18–40 years	Ad lib	Mental stress w/feedback intensity controlled	30 min	ACEi improved
Harshfield et al. (2013)	93 AA adults	Controlled sodium	Mental stress, with monetary incentive	60 min	ARB improved

challenging. From a practical standpoint, there is no reasonable way to identify a salt-sensitive person with administration of a sodium load outside of a research setting. In the office setting, salt sensitivity may be implied if a patient's BP improves with salt restriction. However, this pragmatic approach is complicated by confounding factors, particularly uncertainty about the reliability of adherence. Demonstration of stress-induced sodium retention is an alternative tactic to conventional sodium loading and could allow for a tailored approach to BP control. However, utility has been limited thus far to the research arena, and clinical applicability requires further study. Furthermore, the mechanisms underlying stress-induced sodium retention need further investigation. Reversal of stress-induced sodium retention with renal denervation in animals and with blocking of the RAAS in humans suggests that interplay between these systems results in sodium retention during stress. Further studies exploring the link between the brain and the kidney are indicated.

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## Cross-References

- ▶ [Monogenic and Polygenic Contributions to Hypertension](#)
- ▶ [Neurohumoral and Autonomic Regulation of Blood Pressure](#)
- ▶ [Nonpharmacologic Treatment of Pediatric Hypertension](#)
- ▶ [The Role of Dietary Electrolytes and Childhood Blood Pressure Regulation](#)

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## Part II

# Assessment of Blood Pressure in Children: Measurement, Normative Data, and Epidemiology

Guido Filler and Ajay P. Sharma

## Abstract

The key to diagnosing hypertension in both children and adults involves first accurately measuring the blood pressure and then accurately interpreting the obtained results. In the pursuit of understanding the importance of this measurement and over the course of centuries and countless experiments, first invasive (using arterial lines) and then refined noninvasive methods for measuring blood pressure were developed. In a contemporary clinical outpatient setting, unless a research study requires patients to have their blood pressure measured according to a specific procedure, a sphygmomanometer is applied to a patient when he or she is at rest; this is referred to as “casual or office blood pressure.” In the following chapter, we will review current methods employed to measure casual blood pressure and identify their advantages, disadvantages, and pitfalls.

## Keywords

Aneroid • Auscultation • Beat-to-beat variability • Casual blood pressure • Interpretation of casual blood pressure • Korotkoff sounds • Observer • Oscillometry • Sphygmomanometer • Validation

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## Introduction

- Casual BP measurement is the most commonly used method to identify patients with hypertension. The key to correctly diagnosing hypertension is to obtain a correct casual BP measurement.
- The procedure of measuring casual BP can be broken down into three components:

the device, the patient, and the observer. The device that is used to measure BP is important, considering the variability in results obtained by using different instruments. Mercury sphygmomanometers have been used for decades and are still the gold standard because of their accuracy. Unfortunately, the perceived occupational health danger associated with their use of mercury outweighs their clinical usefulness, which has prompted the development of aneroid and oscillometric techniques. The former is prone to equipment error due to recalibration issues and observer error arising from inadequate personnel training and incorrect identification of the Korotkoff sounds. The latter is much easier to use and produces consistent results, but its dependence on proprietary formulae for calculation of BP rather than directly measured BP limits its ability to compare values obtained between different devices. Once the device is chosen, the observer must select the correct cuff size for the patient, otherwise the measurements may end up inaccurate.

- Aside from the device, the onus is on the observer to ensure that the patient is at rest and in a correct position for measuring BP. Any external or previous factors that could affect the measurement should be identified and addressed to the best of the observer's ability. The observer should also be aware of any observer-based factors that may influence the measurement.
- If the BP measurement is elevated using an oscillometric device, current guidelines recommend that it should be rechecked using an auscultatory method. Unless the patient's BP level is significantly elevated and warrants urgent treatment, elevated BP measurements should be documented on multiple occasions before establishing a hypertension diagnosis in a child.
- Once the BP measurement has been obtained, the observer can use electronic tools to calculate z-scores and to identify the exact percentile of the patient's BP reading. The observer will then be able to define the patient's hypertension by placing it into a specific category ranging from normal BP to Stage 2 hypertension, without any

ambiguity regarding the cut-offs for the ranges. Furthermore, technological advances and the availability of apps on handheld devices have further simplified the process of interpreting BP measurements.

- A wider application of these strategies can play an important role in reducing the underdiagnosis of pediatric hypertension, which can have significant health-care implications considering the evolving obesity epidemic and tracking of pediatric hypertension to adulthood.

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## Background – Past and Present

### Definition

The casual blood pressure is the sum of the relatively stable basal pressure taken under defined conditions of rest and the labile supplemental pressure (casual minus basal), which represents the response to the current degree of physical, mental and probably metabolic stimulation (Smirk 1976).

While the Egyptians had been indirectly measuring one of the most important vital signs by palpating the pulse (Nunn 1996), Hale was the first to directly measure arterial blood pressure (BP) by conducting experiments in horses. He used a fixed glass tube and described that “the blood rose in the tube 8 feet 3 inches perpendicular to the heart: and when it was at full height, it would rise and fall at and after each pulse 2, 3 or 4 inches. . . (Booth 1977).” This crude technique was of course later refined; however, it took until 1855 for someone to invent a noninvasive method that could be implemented in a clinical setting. That someone turned out to be Vierordt (Roguin 2006), who developed a sphygmograph, a cumbersome apparatus that required careful balancing of weights and counterweights (Booth 1977). Etienne Jules Marey used counterpressure to overcome the arterial pressure and substantially improved this device in 1860 by enclosing the arm in a glass chamber filled with water, which was connected to both a sphygmograph and a kymograph, recording arterial pulsations in the arm (Booth 1977). Fifteen years later, Samuel Siegfried Karl Ritter von Basch developed an apparatus that utilized

unilateral compression of the artery and could be used on the limbs (Booth 1977). Collaborating with Zadek, they described hypertension in patients with arteriosclerosis. The turning point in this chronicle of events came in 1886, when Scipione Riva-Rocci published his landmark paper, prompting the development of the present-day technique (Martin 1905). Reverting to older experiments with a mercury manometer, he established the principle of applying pressure to the humeral artery to overcome the arterial pressure. His technique involved compressing the circumference of the arm with an inflated rubber bladder in a bag. Recklinghausen later built upon Riva-Rocci's technique by replacing the narrow 5 cm arm band with a 12 cm wide cuff (Booth 1977).

In North America, the new Riva-Rocci cuff was first introduced into clinical practice at the Johns Hopkins Hospital by Cook and Briggs (1903). They did not believe that cuff size influenced the BP reading, so they used a single rubber bladder covered by a canvas case on all of their patients, including patients as young as 2 years old. They expanded our understanding of BP by reporting BP under various circumstances such as shock, hemorrhage, and in obstetrics (Cook and Briggs 1903). Although the measurements reported by all three physicians were obtained by palpating the brachial pulse, Riva-Rocci used a mercury sphygmomanometer almost identical to the one used in routine clinical practice (Roguin 2006). The well-known Bogalusa Heart Study also made use of the mercury sphygmomanometer in children 5 to 14 years of age (Voors et al. 1976).

In 1905, Korotkoff described the sounds heard when a stethoscope was placed under the BP cuff over the brachial artery at the elbow, and the bladder was inflated beyond the palpable brachial pulse pressure and then slowly deflated. This method became the "gold standard" still used today to manually measure BP using the auscultatory method. In this approach, the first audible sounds indicate the systolic BP (Phase I) and disappearance of those sounds indicates the diastolic BP (Phase V) – see *The Stethoscope* (Lewis 1941).

## The Importance of Measuring Blood Pressure

Identifying hypertension (and hypotension) is of great clinical importance. Hypertension is perhaps the single most prevalent public health concern in the Western World and largely underreported (Peterson et al. 2016). The method in which hypertension is approached in adults, where it is defined based on the cardiovascular morbidity and mortality outcomes data associated with a consistent systolic BP  $\geq 140$  mmHg or diastolic BP  $\geq 90$  mm Hg BP level (Lurbe et al. 2016; Rao 2016; James et al. 2014), cannot be used in children. Their increasing age and ever-changing body size makes it impossible to use a single BP level to define pediatric hypertension (Lurbe et al. 2016). Therefore, a child's BP is classified into BP percentiles based on the normal BP distribution in healthy children, stratified according to child's age, sex, and height. Based on a child's BP percentile, the recently released American Academy of Pediatrics guideline on childhood hypertension (Flynn et al. 2017) classifies BP <90th percentile as normal; between 90th and <95th percentile or if BP exceeds 120/80 mmHg up to <95th percentile in teens >13 years old as elevated BP and BP >95th percentile or >130/80 in teens >13 years old as hypertension. Hypertension is further subclassified into stage 1 hypertension and stage 2 hypertension as detailed in the Appendix.

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## Breaking Down the Measurement: Device, Patient, and Observer

### The Device

Rather than providing an exhaustive list of tools for measuring casual BP, this section will instead focus on the most widely used techniques, namely the "gold standard" mercury sphygmomanometer, aneroid sphygmomanometers, and oscillometric techniques. Other techniques with niche applications such as ultrasound techniques or Penaz's photoelectric measurement of BP in the finger

will not be addressed in detail (Elseed et al. 1973). For more information regarding these less-often used methods, please refer to the excellent review written by Ogedegbe and Pickering (2010). Of note, auscultation of the sounds of the brachial artery during conventional sphygmomanometry may be very challenging in some infants and ultrasound Doppler techniques may be used as a last resort to determine these patients’ systolic BP since it is quite reliable (Bhyravavajhala et al. 2015).

**The Sphygmomanometer**

A sphygmomanometer is a device used to measure BP, composed of an inflatable cuff, a bulb, and a manometer. The cuff is placed over the artery and used to collapse and then release the artery in a controlled manner. This device is also known as a BP meter, BP monitor, or BP gauge (Booth 1977). There are two types of sphygmomanometers: mercury and aneroid.

**Choosing the Correct Cuff Size**

The bladder of the BP cuff must be appropriately sized for the arm of the child. Published guidelines list recommended sizes based on the mid-upper arm circumference (UAC) (Pickering et al. 2005). Corresponding ideal cuff sizes are listed in Table 1.

In the interest of simplicity, most centers employ a visual check system using one of three criteria:

- a) The bladder width must be at least 40–50% of the arm circumference.
- b) The bladder length must be at least 80–100% of the arm circumference.
- c) The cuff width must be 66–75% of the acromion-olecranon distance (upper arm length, UAL).

In a survey of 400 hospital- and office-based pediatricians, Arafat and Mattoo from the Children’s Hospital of Michigan found that age usually determines the choice of cuff. That survey included several other surprising results:

- 57% of practitioners would consider using a neonatal cuff for patients up to 1 month of age.
- 65% would use an infant cuff for a one-year-old.
- 49% would use a child/pediatric cuff for a five-year-old.
- 84% would use a small adult cuff for children and adolescents 10 years of age and older.
- 83% would consider using an adult cuff in children 11 years of age and older.

Arafat and Mattoo thus concluded that practitioners were likely to use inappropriately sized cuffs. The recommended and used cuffs differed by two thirds to three quarters of the UAL criteria (overestimating the BP), and too large of a cuff, particularly in older children, by 40% of UAC criteria (underestimating the BP) (Arafat and Mattoo 1999). A due diligence on the part of health care personnel in first ensuring a proper measurement of patient’s arm circumference and then choosing an appropriate-sized cuff

**Table 1** Recommended “ideal” cuff sizes for different age groups. Modified from the National High Blood Pressure Education Program Working Group on high blood pressure in children and adolescents (The fourth report on

the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents 2004) and Pickering et al. (2005)

Patient	Arm Circumference (cm)	Cuff Size (cm)
Newborn	Up to 10	4 × 8
Infant	>10 to 15	6 × 12
Child	15 to 22	9 × 18
Small adult	22 to 26	12 × 22
Adult (standard)	27 to 34	16 × 30
Large adult*	35 to 44	16 × 36
Adult (thigh)*	45 to 52	16 × 42

\*Optimal ratios for arm width and length to circumference are only presented for the small and standard adult cuff sizes, because the ideal width to circumference ratio is not clinically practical for the large adult and thigh cuffs (although the ideal length x circumference ratio is given)

accordingly based on the recommendations shown in Table 1 is important.

### The Mercury Sphygmomanometer

The notable accuracy of mercury devices has led to their classification as the “gold standard.” They indicate BP using a mercury manometer. The manometer consists of a column of mercury, which rises or drops according to the measured BP. Uniquely, this type of sphygmomanometer does not need to be recalibrated. Their high rate of accuracy has elicited their use in pharmaceutical clinical trials and in clinical evaluations of high-risk patients. This instrument has been so influential that current BP pediatric reference intervals are still based on readings from a mercury sphygmomanometer (The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents 2004). The design of mercury sphygmomanometers has hardly changed over the past 60 years; the only improvement in modern versions is their lower likelihood of spilling mercury when dropped. Although the auscultatory method coupled with the use of a mercury sphygmomanometer is still regarded as the “gold standard” when measuring office BP, the widespread occupational safety concerns of instruments containing mercury in North America over the last decade (Messelbeck and Sutherland 2000) continues to diminish the role of this technique (Pickering et al. 2005).

### The Aneroid Sphygmomanometer

Aneroid (meaning “without fluid”) sphygmomanometers were developed as a safe alternative to mercury sphygmomanometers. They are, however, less accurate (particularly those that are less expensive) and often require frequent calibration (Pickering et al. 2005). Rather than employing mercury, the aneroid manometer is based on a metallic pressure-sensing element that flexes elastically under the effect of a pressure difference across the element. Aneroid sphygmomanometers are commonly used in community pediatricians’ offices and in pediatric hospital outpatient units. Aneroid manometers are quite accurate when calibrated on a semiannual basis (Canzanello et al. 2001). The Fourth Report

recommends aneroid manometers when mercury column devices cannot be obtained (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004).

### The Stethoscope

Auscultation employing manual sphygmomanometers (mercury or aneroid) requires a stethoscope. Although the manual method that employs a mercury sphygmomanometer and stethoscope remains the “gold standard” to this day, this technique is technically demanding and operator-dependent. While automatic devices have advanced and simplified technical standards, a standardized procedure that produces comparable results has yet to be developed (Vischer and Burkard 2016). Obviously, the quality of the stethoscope makes a difference (see observer errors below).

In the manual method, the stethoscope is placed over the brachial artery and the observer listens to the Korotkoff sounds (Beevers et al. 2001). There are five phases to listening to the Korotkoff sounds:

- Phase I** – The first appearance of faint, repetitive, clear tapping sounds, which gradually increase in intensity for at least two consecutive beats. This indicates the systolic BP.
- Phase II** – A brief period may follow during which the sounds soften and acquire a swishing quality.
- Phase III** – The return of sharper sounds, which become crisper to regain, or even exceed, the intensity of Phase I sounds.
- Phase IV** – The distinct abrupt muffling of sounds, which become soft and blowing in quality.
- Phase V** – The point at which all sounds finally completely disappear indicates the diastolic pressure.

Of note, Phase II and III are of limited clinical importance. Korotkoff originally recommended using Phase IV as the diastolic pressure (Beevers et al. 2001), and the use of Phase IV versus Phase V for diastolic pressure has been a point of



contention in the medical community for many years. The value of Phase IV (muffling) can be up to 10 mmHg higher than the value of Phase V (disappearance), although the difference is usually less than 5 mmHg. It is important to note that Phase V correlates best with intra-arterial pressure (Beevers et al. 2001). Phase V has been recommended for diastolic BP since the 1996 Working Group Report. Only if very low phase V persists or there is difficulty determining it (as sometimes occurs in children) should phase IV be recorded as the diastolic BP (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004).

### Oscillometric Devices

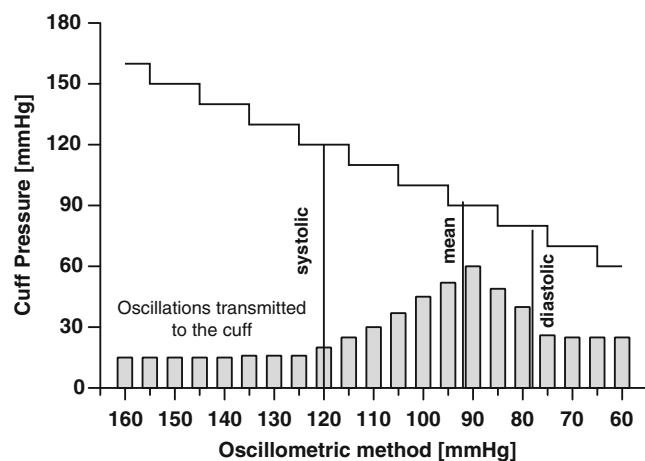
Despite the advantage of providing an accurate BP assessment, observer bias (discussed later) and pronounced white coat effect (induced by observer's presence) are important limitations of auscultatory BP method. Learning and employing the technique of auscultatory BP measurement can be labor-intensive and may restrict its use in clinical practice (Flynn 2016). Automated BP measurement by oscillometric devices offers an alternative to auscultation. The oscillometric method was first demonstrated in 1876 and involves the observation of oscillations in the pressure of the sphygmomanometer cuff (Pickering et al. 2005). This method measures the oscillations of blood flow instead of Korotkoff

sounds. Oscillometric BP technique uses a cuff transducer to detect and send changes in amplitude of arterial wall oscillations to a microprocessor. An oscillometric device will roughly recognize the following (see Fig. 1):

1. The device starts perceiving oscillations when the artery compression is slowly released. The oscillations increase in amplitude as cuff pressure falls, with a peak close to mean arterial pressure (MAP), followed by the decrease in the amplitude as cuff pressure drops below MAP. MAP divides the oscillation envelope into rising and falling phases.
2. Using the device-specific algorithm, characteristic ratios or fractions of the peak amplitude are used to find points corresponding to systolic pressure on the rising phase of the envelope and diastolic pressure on the falling phase of the envelope.

Oscillometry is often used in automatic BP devices because it does not contain mercury and has reduced observer error with regard to identifying the Korotkoff sounds. It is important to note that, unlike auscultatory methods, oscillometric methods employ software in the device that must estimate the BP since the Korotkoff sounds do not emit any specific oscillations. Each manufacturer uses a different algorithm in its software to perform these estimations. Most oscillometric

**Fig. 1** The principle of the oscillometric method



algorithms start by measuring the mean arterial pressure (MAP) and then the pulse pressure (PP) according to the threshold of the device. From there, the algorithms approximate the diastolic BP ( $MAP - 1/3(PP)$ ) and systolic BP ( $MAP + 2/3(PP)$ ). PP is the difference between the systolic and diastolic BP. Due to the difference in the measurement techniques, BP obtained by oscillometric method and auscultation can differ. Some studies found that oscillometric results were 2 mmHg lower for systolic and 1.3 mmHg lower for diastolic BP than the results obtained using the auscultatory “gold standard” method (Landgraf et al. 2010; Zheng et al. 2011). The study in children by Park et al., however, found that the oscillometric technique tends to produce higher measurements compared to auscultation. The two can differ by as much as 10 mm Hg for the systolic and 5 mm for the diastolic BP (Park et al. 2001). MAP measurements had the best agreement between the two methods (Zheng et al. 2011). This difference in BP measurements becomes clinically important as the Fourth Report BP thresholds (The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents 2004), which are commonly used to interpret BP in practice, were created using auscultatory measurements. Preliminary observations have shown that understanding the variations in the shape of oscillometric waveform could be a way to improve the agreement between the two techniques. At this point, more work is needed to classify different waveform shapes and to understand the effect of age and patient characteristics on these waveforms (Amoore et al. 2008). Deciphering the methods to address the confounding effect of patient characteristics such as pulse pressure and arterial stiffness on the oscillation ratios, employed to estimate systolic and diastolic BP from MAP, can further improve the accuracy of oscillatory BP measurements (Forster and Turney et al. 1986; van Popele et al. 2000). Device algorithms must be developed using large patient populations because some medical conditions, such as pediatric obesity and diabetes, may affect oscillometric BP readings. A large, recent Korean population-based study found no association between sex,

age, and BP medication and the difference in interarm BP (Song et al. 2016).

Their lack of mercury and the ease of use have prompted the gradual switch from auscultatory sphygmomanometers to oscillometric BP devices over the past two decades. This method does, however, harbor some challenges, particularly in children (Chiolero et al. 2010). Motion artifacts induced by their emotional lability and difficulty staying still hamper the BP accuracy in younger children. About one third of children who had BP readings >90th percentile at the beginning of their clinic encounter had normal BP at the end of the encounter (Tschumi et al. 2011). Newborns and other special populations may require specific algorithms (Nelson et al. 2002). Of the few good studies that compared different devices in children and adolescents, some suggest that there are substantial differences between the different devices (Wong et al. 2006). Only a few reference intervals have been published in the pediatric literature (Narang et al. 2015), and those that are most accurate will have to be specific to the device with well-defined normative populations (Chahine et al. 2015). Device-specific proprietary algorithms also limit the development of universal oscillometric normative BP thresholds (Krmr et al. 2015). Furthermore, the difference between oscillometric and aneroid BP values can be aggravated in certain population groups such as those with chronic kidney disease (CKD). In CKD patients, for example, Flynn and colleagues noticed that both systolic and diastolic BP readings were significantly higher using an oscillometric device than with an aneroid sphygmomanometer (Flynn et al. 2013).

Despite some limitations, automated oscillometric BP technology still has several advantages, mainly its ease of use and less human error because of observer bias or hearing impairment. In order to obtain the most accurate results, the onus is still on the observer to apply a correctly sized cuff at the correct location on the limb, and to ensure that the patient is properly seated and calm. Obtaining 2–3 readings, excluding the first high reading because of the white coat effect and averaging the other BP readings, can improve the accuracy of BP measurements.

Newer oscillometric devices such as Bp TRU™ offer the benefit of reducing the white coat effect by virtue of automatic BP measurement without an observer's presence, resulting in an increase in the use of these devices in clinical trials and other settings (Myers et al. 2012).

## The Patient

Insofar as is practical, the patient should be relaxed in a quiet room at a comfortable temperature, seated comfortably, and a short period of rest should precede the measurement. Ideally, this period of rest is 5 minutes in length. There is some natural beat-to-beat variability at rest that accounts for approximately 4 mmHg (Parati et al. 1989). Recent ingestion of pressure-influencing substances (caffeine, medications) and talking may also affect the BP reading. Any factors beyond these optimum conditions should be noted with the BP reading in the patient's chart, for example, "BP 154/92, R arm, V Phase" (patient very nervous) (Beevers et al. 2001). There is some controversy as to whether the patient should be seated or supine, but most guidelines recommend that the patient be seated with their back supported and both feet on the floor (Petrie et al. 1986; Pickering et al. 2005).

## Effects of Posture and Support

Multiple factors affect the BP measurement, including inherent BP variability, the defense reaction, the limitations of the device being used to take the measurement, the accuracy of the device, and inherent limitations in special populations such as infants and small children.

**Posture** may affect BP since it has a tendency to increase when the patient switches from the lying to the sitting or standing position. Therefore, the posture of the patient should always be consistent. The patient should be comfortably seated and his or her arm must be supported at the level of the heart. While there is no strict guideline as to the length of time that the patient should be at rest, the consensus suggests a minimum of 3 minutes (but ideally 5 minutes) of rest before BP is measured. If the patient has postural hypotension, whether caused

naturally or through the use of certain medications, his or her BP should be measured in both the lying and standing positions (Beevers et al. 2001).

**Arm support** is also very important; the arm should always be supported when BP is measured. If the BP is taken when the arm is unsupported, the isometric activity in the limb may raise the heart rate and BP. The diastolic BP may rise by as much as 10% if the arm is unsupported and extended, an effect that may be magnified in patients with hypertension and in those taking beta blockers. To support the arm, the observer can hold the subject's arm at the elbow or the patient can rest his or her arm on a stool or armrest (Beevers et al. 2001).

**Back support** is also important; the back must always be supported during the measurement. Cushman et al. showed that patients who sit bolt upright may have a diastolic BP that is up to 6.5 mmHg higher than patients who sit back (Cushman et al. 1990).

The **position of the arm** is also very important. The arm must be horizontal and kept at the level of the heart as denoted by the midsternal line. If the arm is moved down from the horizontal to the vertical position, the BP increases by up to 6 mmHg (Ogedegbe and Pickering 2010).

In inpatient settings, especially in the NICU, nurses often use whichever limb they can access to obtain the BP. Patients are typically supine. Few studies address this topic, and the results of those that have been published are both conflicting and often methodologically unsound. None of the studies have randomized the selection of the limb. One study, which provided a mixed analysis of variance, found that the choice of limb significantly affected the diastolic BP (Tran et al. 2014). Since the exact effect of the choice of limb is understudied, it is very important to note which limb is used to measure a child's BP. Crapanzano observed that age was influential when comparing arm and calf BPs. Systolic, diastolic, and mean calf BP were lower than the arm pressures until the age of 6 months when the values were most equivalent, then calf BP exceeded arm BP (Crapanzano et al. 1996). In neonates with normal echocardiograms, the BP variation between the limbs was found to be large enough questioning

the usefulness of BP difference between the limbs for suspecting coarctation of aorta (Crossland et al. 2004). In PICU setting, calf and arm oscillometric BPs differ markedly in children older than 1 year through 8 years, with the difference being large in children between ages 2 and 5 years (Schell et al. 2011). Park and Lee did not find an effect of gender and ethnicity on arm-calf differences (Park and Lee 1989). If the calf BP is unavoidable due to medical reasons, a consistency in the BP measuring technique, maintaining limbs at heart level in supine children, selection of an appropriate-sized cuff based on limb circumference, and documentation of BP site in the medical record to use the same site can improve the consistency of BP recordings.

### **Cuff-Inflation Hypertension**

Intra-arterial measurements have shown that the act of inflating the cuff does not in itself change the BP (Parati et al. 1985). However, one study by Mejia et al. showed that there may be a transient increase in the BP of occasional patients of up to 40 mmHg that coincides with the inflation of the cuff (Mejia et al. 1990). Although the topic is understudied, the authors believe that this phenomenon is particularly important in infants. The only pediatric literature that has been published on this topic employed the use of an oscillometric device for a different purpose (Alpert 2011). This phenomenon appears to be independent from white coat hypertension, where the rise in BP both precedes and outlasts the inflation of the cuff (Ogedegbe and Pickering 2010). Finally, self-measurement may cause a transient increase in BP, likely due to the patient's muscular contractions when inflating the cuff.

### **White Coat Hypertension**

A 40-year-old study by Ayman and Goldshine revealed the effect of measuring BP in a physicians' office ("white coat hypertension"), a phenomenon that could increase a patient's BP by as much as 30 mmHg when compared with the patient's own measurement at home, even when employing the same technique and the same posture. It is important to distinguish between true hypertension and white coat hypertension.

Previously defined as the difference between the clinic and daytime ambulatory or home BP (Verdecchia et al. 1995), white coat hypertension is characterized by an increase in BP at the clinic visit and normal BP at home. The underlying mechanisms that are thought to contribute to this effect include anxiety, a hyperactive alerting response, and/or a conditioned response (Jhalani et al. 2005). To some extent, the white coat effect is seen in almost all hypertensive patients and is usually either much less pronounced or absent in normotensive individuals. Only ambulatory BP monitoring or home self-monitoring can reliably diagnose white coat hypertension, as described later in this textbook. Physicians also tend to record higher pressures when employing aneroid techniques than nurses or technicians (Ma et al. 2009). The cardiovascular morbidity of patients with white coat hypertension is slightly higher than in patients with normotension but much lower than in patients with true sustained hypertension (Briasoulis et al. 2016). Correctly diagnosing white coat hypertension is therefore paramount to avoiding overtreating patients and potentially exposing them to serious adverse drug reactions (Briasoulis et al. 2016).

### **The Observer**

The observer (physician, nurse, or technician taking the BP measurement) must be aware of the considerable moment-to-moment variability in BP that occurs alongside respiration, emotion, exercise, eating, conversation, tobacco, alcohol, ambient temperature, bladder distension, and pain. They must also be aware that BP is influenced by age, gender, race, and circadian variation (McCubbin et al. 1991), and they should inquire about any recent exercise. Falsely low diastolic readings (Gould et al. 1985) and falsely high systolic readings can usually be observed in the recovery phase following exercise (Gould et al. 1985; Henschel et al. 1954). BP is usually at its lowest during sleep. Although it may not always be possible to eliminate many of these effects, observers can try to minimize their effect by taking these factors into account in their

measurement when possible (Beevers et al. 2001). In principle, observer errors can have a positive, neutral, or negative effect on the BP reading. Technical errors may also affect the measurement, especially if an aneroid BP monitor is employed. Past publications have demonstrated frequent inaccuracy in these apparatuses (Burke et al. 1982); however, aneroid manometers are reported to be quite accurate when calibrated on a semiannual basis (Canzanello et al. 2001).

### Observer Bias

Intra and interobserver error can also introduce systematic errors. Lack of concentration, poor hearing, confusion, and auditory or visual distractions may all lead the observer to incorrectly interpret the Korotkoff sounds, especially with regard to the diastolic pressure (Rose 1965). Despite its many limitations, the ability to circumvent these sources of error is one of the main advantages of oscillometric devices. The observer may also have an inherent bias or prejudice. Knowingly or unknowingly, the observer adjusts the pressure to meet his or her preconceived notion of the BP measurement the patient should have. This usually occurs when the observer is reluctant to diagnose hypertension (Beevers et al. 2001). An observer may want to record a favorable measurement in a healthy, slender adolescent with borderline increases or may overread BPs in an obese adolescent with type II diabetes mellitus. Another important bias is related to what is known as “terminal digit preference.” One study demonstrated that doctors have a tendency to round the last digit to zero. In fact, physicians may have a 12-fold bias that favors zero, a bias that could significantly affect his or her decision to diagnose and treat the patient (Niyonsenga et al. 2008). The position of the observer is also important – he or she should be in a comfortable and relaxed position, because deflating the cuff too quickly may underestimate the systolic and overestimate the diastolic BP (see below) (King 1963).

### Cuff Size

Having already alluded to the utmost importance of choosing the appropriate cuff size, it is

important to reiterate that the most common mistake observers (and especially pediatricians (Arafat and Mattoo 1999)) make is to use a cuff that is too small for the patient. Doing so overestimates the BP (Maxwell et al. 1982). To determine the appropriate size of cuff based on the patient’s arm circumference, please refer to Table 1.

### Diurnal Variation

Diurnal variability has a pronounced effect on BP, which decreases by 10–20 mmHg during sleep and significantly increases upon waking. BP is typically at its highest between 6 a.m. and noon. This is also when morbid cardiovascular events are most prevalent (Muller et al. 1997). This phenomenon may be a by-product of the morning endogenous cortisol peak. The observer should therefore make note of the time of day that the casual BP is measured.

### Cuff Inflation and Deflation Rate

For the most part, the rate at which the cuff is inflated has no bearing on the BP measurement (King 1963). A very slow rate of inflation (less than 2 mmHg/second), however, diminishes the intensity of the Korotkoff sounds and results in a slightly higher diastolic BP (Imai et al. 1989). The recommended deflation rate is 2–3 mmHg per s.

### Auscultatory Gap

Korotkoff sounds may disappear and reappear as the cuff is being deflated without the presence of any cardiac arrhythmias. If the observer does not recognize this gap, the diastolic BP may read as falsely high while the systolic BP may appear falsely low. This phenomenon is more commonly seen in patients with faint Korotkoff sounds such as infants (Bhyravajhala et al. 2015). While understudied in children, recognizing the presence of the auscultatory gap may be very important because of its described association with increased arterial stiffness (Cavallini et al. 1996). Early loss of audible sound in auscultatory gap is thought to be due to blunted high-frequency phase II signal, likely related to altered physical properties of a stiffer arterial wall. Palpatory estimation

**Table 2** A summary of the factors that affect blood pressure

Effect on BP	Patient factor	Observer factor
<b>Predominantly increases</b>	<ul style="list-style-type: none"> <li>• Male sex</li> <li>• Older age</li> <li>• Overweight or obesity</li> <li>• Dietary salt intake</li> <li>• Sleep disturbance</li> <li>• Recovery phase following exercise (systolic)</li> <li>• Stress (white coat hypertension)</li> <li>• Inflation of the cuff in some occasional patients (cuff-inflation hypertension)</li> <li>• Self-measurement</li> </ul>	<ul style="list-style-type: none"> <li>• Time of day (between 6 a.m. and noon)</li> <li>• Use of too small of a cuff</li> <li>• The patient's arm is placed below the midsternal line</li> <li>• The patient's arm is not supported (diastolic)</li> <li>• The patient is sitting bolt upright rather than sitting back (diastolic)</li> <li>• Use of the Phase V rather than Phase IV Korotkoff sound to identify the diastolic pressure in children</li> <li>• The auscultatory gap is not identified if present (diastolic)</li> </ul>
<b>Increases or decreases</b>	<ul style="list-style-type: none"> <li>• Family history</li> <li>• Ethnicity</li> <li>• Underlying medical condition (can be genetic)</li> </ul>	<ul style="list-style-type: none"> <li>• Personal bias</li> <li>• The choice of limb (diastolic)</li> <li>• Using an oscillometric device</li> <li>• Misidentification of the Korotkoff sounds</li> <li>• Calculation of percentiles (directly using the Fourth Report tables vs. calculating the z-scores)</li> </ul>
<b>Predominantly decreases</b>	<ul style="list-style-type: none"> <li>• Sleep</li> <li>• Lying down</li> <li>• Recovery phase following exercise (diastolic)</li> <li>• Postural hypotension</li> </ul>	<ul style="list-style-type: none"> <li>• Overly rapid deflation of the cuff</li> <li>• Use of too large of a cuff</li> <li>• The auscultatory gap is not identified if present</li> </ul>

of systolic BP while inflating the BP cuff and inflating the BP cuff higher than the pulse obliteration pressure can eliminate the auscultatory gap.

Taken together, the observer must be made aware of numerous patient and observer factors that influence BP when striving to accurately diagnose hypertension. A comprehensive list of these factors can be found in Table 2.

## Interpreting Casual BP

Measuring casual BP is the most widely used method to screen and diagnose patients for hypertension. For an accurate BP measurement, it is important to avoid technical, patient-related, and observer-related errors. High BP should also be confirmed on repeated visits before characterizing a child as having hypertension. High BP tends to settle down in many children on repeat testing as a result of the patient relaxing and thus if one measurement is extreme, another will tend to fall closer to the average. When attempting to determine the prevalence of high BP in population-based studies, it is important to understand that

unlike in adults, childhood hypertension is defined based on statistically derived nomograms rather than on clinically significant outcomes such as heart failure, stroke, or death. As a result, the BP threshold used to define high BP can influence the prevalence of hypertension. While analyzing NHANES data, Kit et al. (2015) used BP percentiles from the Fourth Report (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). In contrast, Rosner et al. (2013) used lower BP percentiles derived from normative data that only included children of a normal weight. Moreover, the racial distribution in a population can also influence the prevalence of hypertension. In 2011–2012 NHANES data, the prevalence of high BP (hypertension and prehypertension) varied across different races, with a prevalence of 8.5% in Asian children as compared with 9.4% in whites, 11.5% in Hispanics, and 15.3% in blacks (Kit et al. 2015). A similar racial distribution was also noticed in previous 1999–2002 NHANES data, with a prevalence of high BP in 9.1% whites, 10.9% Hispanics, and 12.8% blacks (Din-Dzietham et al. 2007).

Unless specific reference intervals for a given device and a given population are available (Chahine et al. 2015), the authors recommend using normative BP values derived from the National High Blood Pressure Education Program (NHBPEP) database. It is important to note that the NHBPEP reference tables are derived from auscultatory BP measurements using a mercury sphygmomanometer. Due to the difference in the oscillatory and auscultatory BP measurements, elevated oscillatory measurements should be rechecked using an auscultatory method. Adequate diligence to stick to recommended cuff size and procedural details for BP check, confirming elevated oscillatory BP by auscultation, and repeating BP at later encounters are key details for establishing an accurate diagnosis of hypertension (Flynn 2013).

The Fourth Report BP tables consist of multiple BP thresholds that take the subject’s age, gender, and height into account. Although useful, complexity of navigating through multiple BP thresholds has impeded their use in clinical practice, resulting in a significant underdiagnosis of pediatric hypertension (Adroque and Sinaiko 2001; Brady et al. 2010; Hansen et al. 2007). Consequently, clinicians have proposed the use of simplified BP tables that contain fewer BP thresholds (Mitchell et al. 2011; Kaelber and Pickett 2009). Their ease-of-use makes simplified BP tables a useful screening tool for improving the interpreting pediatric BP measurements in a clinical setting (Zuijdwijk et al. 2013; Sharma et al. 2015). The simplified table recently published in the 2017 AAP guideline (Flynn et al. 2017) is the first such table to be endorsed by a

consensus organization. Box-Cox transformations have also been used to calculate gender, age, and height-independent z-scores (He et al. 2003). Banker et al. developed BP charts representing BP percentile curves to improve screening for both high and low BP in children similar to the growth charts developed by the CDC and the WHO (Banker et al. 2016). These charts have been made available to the public on PubMed Central and can be downloaded in high definition at <https://med.uth.edu/pediatrics/files/2013/07/BPChartBoyscolorwide.pdf> for boys and at <https://med.uth.edu/pediatrics/files/2013/07/BPChartBoyscolorwide.pdf> for girls. Physicians may find it easier to use software on handheld devices such as STAT GrowthCharts by Austin Physician Productivity, LLC. They use the same approach and provide BP percentiles. Some “apps” for handheld devices are listed in Table 3. They have all been developed using the Fourth Report tables (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). At the time of publication of this book, apps based on the 2017 AAP guideline were not yet available.

N.B.: The apps either provide percentiles or z-scores. Z-scores are a means of expressing the deviation of a given measurement from the size- or age-specific population mean. Serial measurements and longitudinal data comparisons in pediatric nephrology practices are best charted using z-scores because they take growth and age into account. Since they can be applied to BP, they are a useful tool for assisting with clinical decision-making (Chubb and Simpson 2012).

**Table 3** Some examples of smartphone applications that calculate gender-, age-, and height-specific percentiles for casual BP measurements

Program name	Software company	Platform(s)
STAT GrowthCharts	Austin Physician Productivity, LLC	iPhone, Android
Ped(z)	Department for Pediatric and Adolescent Medicine, University of Erlangen, Germany	iPhone, Android, Windows phone, Web app
Body composition laboratory*	USDA/ARS Children’s Nutrition Research Center, Houston, Texas	Web app

Available at: \*<https://www.bcm.edu/bodycomplab/Flashapps/bmiVAgeChartpage.html>, <http://www.quesgen.com/BMIPedsCalc.php>

## Conclusion

The gold standard instrument used to measure BP is still a mercury sphygmomanometer with an appropriately sized cuff. Nevertheless, they are becoming scarcer as they are phased out due to concerns about the safety of mercury and the observer errors that can arise with their use. Aneroid and oscillometric devices are now more commonly used, but the former require frequent calibration and are still associated with observer errors, and oscillometric devices rely on calculated systolic and diastolic BP and lack oscillometric-based reference tables. Physicians must be mindful of inherent biases associated with any of these tools. For an appropriate interpretation of BP values thresholds, an auscultatory BP confirmation is important. The simplified BP table in the new guideline (Flynn et al. 2017) can help identify BP values that need to be compared to the full table of normative values. For improving the accuracy of BP measurements, it is important to maintain a quality control and reasonable standards for training the observers, adopting correct BP measurement technique, and ensuring the use of appropriate cuff and equipment (Campbell et al. 2016).

## Cross-References

- ▶ [Cardiovascular Influences on Blood Pressure](#)
- ▶ [Development of Blood Pressure Norms and Definition of Hypertension in Children](#)
- ▶ [Diagnostic Evaluation of Pediatric Hypertension](#)
- ▶ [Epidemiology of Primary Hypertension in Children](#)
- ▶ [Ethnic Differences in Childhood Blood Pressure](#)
- ▶ [Hypertensive Models and Their Relevance to Pediatric Hypertension](#)
- ▶ [Methodology and Applicability of Home Blood Pressure Monitoring in Children and Adolescents](#)
- ▶ [Neonatal and Infant Hypertension](#)
- ▶ [Obesity Hypertension: Clinical Aspects](#)
- ▶ [Sequelae of Hypertension in Children and Adolescents](#)
- ▶ [The Role of ABPM in Evaluation of Hypertensive Target-Organ Damage](#)
- ▶ [The Role of Dietary Electrolytes and Childhood Blood Pressure Regulation](#)
- ▶ [Value of Routine Screening for Hypertension in Childhood](#)

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# Value of Routine Screening for Hypertension in Childhood

Michael G. Semanik and Joseph T. Flynn

## Abstract

Many consensus organizations recommend that all children have their blood pressure routinely measured to screen for hypertension. The value of this practice has been questioned based upon a lack of conclusive clinical trial evidence that such routine measurements lead to prevention of adult cardiovascular disease. Additionally, even recognizing elevated blood pressure measurements in childhood can be challenging, which may further weaken the value of routine blood pressure screening. However, ample indirect evidence from longitudinal cohort studies exists that elevated blood pressure early in life is linked to intermediate end points and may predict the development of adult hypertension. Additionally, elevated childhood blood pressure may be an early sign of an underlying condition that requires specific treatment. The rationale for routine

blood pressure screening in childhood will be discussed in the context of these important issues.

## Keywords

Screening • Guideline • Cardiovascular disease • Secondary hypertension • Electronic health records

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## Introduction

Pediatric hypertension is no longer a rare problem. Its prevalence has climbed steadily over the past several decades (Din-Dzietham et al. 2007; Flynn 2013), such that today's primary care providers will almost certainly encounter hypertensive children and adolescents should they decide to look. The central question this chapter addresses is whether or not they *should* look. More formally, it considers the question "does the early identification and treatment of pediatric hypertension provide benefits to patients?"

For adults, this question has long been answered in the affirmative. Multiple iterations of the Joint National Committee, including the recent report of the JNC 8 committee members (James et al. 2014), have recognized hypertension as a significant risk factor for cardiovascular morbidity and mortality. Thus, adults routinely have their blood pressure (BP) screened, and adult hypertensives, once identified, are actively monitored and treated. Many other adult guidelines endorse this approach, such as those from the American Diabetes Association (2016), the American College of Cardiology Foundation and American Heart Association (Aronow et al. 2011), and the European Societies of Hypertension and Cardiology (Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and Task Force for the Management of Arterial Hypertension of the European Society of Cardiology 2013). This has resulted in a general consensus that, in adults, hypertension is a disease requiring treatment.

Unfortunately, no such consensus exists in pediatrics. In fact, national expert committees contradict each other outright, with some recommending routine BP screening for children and others dismissing the practice as a waste of time and money. The discrepancy between adult and pediatric views of BP screening arises from a lack of hard evidence: there is no study that conclusively links elevated childhood BP with an increase in mortality for either those children or the adults they will become. From this perspective it could be said that pediatric hypertension has not

been conclusively proven to be a specific disease with long-term consequences.

A lack of direct evidence, however, does not imply no evidence at all. Much indirect evidence does exist, the majority of which suggests that hypertensive children become hypertensive adults with the increased morbidity and mortality that entails. After a brief examination of the challenges facing recognition of pediatric hypertension, this chapter will explore this evidence in detail. We will also elucidate how the various expert panels charged with determining the utility of pediatric BP screening reached opposite conclusions. The potential benefits of BP screening, including its use in diagnosing secondary hypertension, will then be examined. Finally, we will present recommendations for future study, in hopes that one day the question of whether or not pediatric hypertension is an actual disease process with consequences in adulthood will be definitively answered.

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## Recognizing Pediatric Hypertension Can Be Challenging

Any discussion of pediatric hypertension screening must begin by acknowledging that pediatric hypertension is significantly underdiagnosed. This was first demonstrated in a landmark study by Hansen et al. (2007), who showed that 74% of children meeting the criteria for hypertension during a well-child visit went unrecognized. This percentage increased to 87.5% in a paper by Brady et al. (2015), who considered children presenting for both preventative care and acute care visits. These findings have been confirmed in multiple other studies (Stabouli et al. 2015; Aliarzadeh et al. 2016; Shapiro et al. 2012), with recognition rates ranging from 5% to 67%. It is clear, then, that a large number of children who meet criteria for hypertension go unrecognized.

Various explanations for this underrecognition have been proposed. Some focus on the complexity involved in diagnosing hypertension in childhood (Brady et al. 2010; Mitchell et al. 2011) – making the diagnosis requires triangulating a patient's age, sex, and height onto percentile tables – whereas others attribute it to the

increasing time pressures on primary care providers (Cha et al. 2014). These problems are compounded when one considers that the diagnosis of hypertension in childhood requires that a patient's BP exceed a certain threshold on more than one occasion. Simply discovering previous values for a patient's BP may increase both the complexity and duration of an office visit; never mind the additional calculations needed to determine whether past BPs were normal or elevated.

Fortunately, there are encouraging signs that the use of electronic health records (EHRs) may increase the rate at which pediatric hypertension is diagnosed. Not only can EHRs automatically determine an individual patient's threshold for hypertension and easily access past BP measurements, but they can also send providers alerts when hypertension is diagnosed. In the 2015 Brady paper, hypertension recognition increased from 12.5% to 42% when EHR alerts were implemented. Although the majority of hypertensive children still went unrecognized, this represents a significant improvement.

Why so many hypertensive children still went unrecognized in the Brady study despite an EHR performing all of the calculations necessary to identify elevated BP readings is an interesting question. Further detailed investigation of this phenomenon is needed, but one explanation may lie in the conflicting recommendations of expert committees. The fact that experts disagree as to whether or not children should have their BPs checked regularly may discourage some primary care providers from reacting to positive screens or from screening entirely.

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## Different Points of View

Recommendations regarding pediatric hypertensive screening come primarily from North America and Europe. However, neither continent has been able to agree on the sphygmomanometer's utility as a screening tool. Guidelines published by the European Society of Hypertension (Lurbe et al. 2016) recommend at least annual BP screening for all children aged 3 years and older, whereas the United Kingdom recommends

against universal screening (United Kingdom National Screening Committee 2011). Recommendations from the United States, issued by two federal expert committees, are equally divided. Favoring universal screening, the Task Force on Blood Pressure Control in Children of the National Heart, Lung, and Blood Institute (NHLBI) has recommended at least annual BP measurement in all children 3 years of age and older since the First Task Force Report was released in 1977 (Blumenthal et al. 1977). The NHLBI reaffirmed this position in their integrated guidelines for cardiovascular disease prevention (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents and National Heart, Lung, and Blood Institute 2011) which largely repeated recommendations for BP measurement found in the Fourth Task Force Report (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). As reviewed in the Appendix, a similar recommendation for routine BP measurement starting at the age of 3 is also found in the 2017 guidelines issued by the American Academy of Pediatrics (AAP). However, since 2003 the US Preventive Services Task Force (USPSTF) has found insufficient evidence to recommend for or against BP screening in children and adolescents (U.S. Preventative Services Task Force 2003). This "I recommendation" was reaffirmed after an updated review of the evidence in 2013 (Thompson et al. 2013), ensuring that the discrepancies found in these federal reports remain unresolved.

Compounding this disagreement, the two largest professional societies representing pediatric primary care providers in the United States have also taken opposite sides of the debate. The AAP's Bright Futures™, created in the mid-1990s as a universal guideline for preventative pediatric care, has incorporated the NHLBI's recommendation for routine BP screening. When Bright Futures™ was adopted by the AAP in the mid-2000s, this became de facto AAP policy as well. Indeed, the third edition of Bright Futures™, published under the auspices of the AAP in 2008, continues to promote at least annual BP measurements

(Hagan et al. 2008). However, in keeping with long-standing policy, the American Academy of Family Physicians (AAFP) has adopted the USPSTF position and therefore does not recommend screening BP measurements in children under the age of 18 years (U.S. Preventative Services Task Force 2015). Family medicine providers are not necessarily discouraged from checking children's BP but are warned about the possibility of false-positive readings. Ultimately, the choice of whether or not to screen a given child for hypertension is left to the individual family practitioner.

For primary care providers, this is admittedly a perplexing state of affairs. How can thorough reviews of the evidence, performed by both the NHLBI and USTSPF, reach almost opposite conclusions? How can it be that pediatricians are directed to screen for hypertension, but family medicine providers are allowed not to?

The answer lies in the guiding principles of each committee's review. The overarching goal of the USPSTF was to "determine the balance of benefits and harms of routine screening for high BP in children and adolescents" (Thompson et al. 2013). Similarly, the NHLBI Working Group saw as its mandate "to provide recommendations for diagnosis, evaluation, and treatment of hypertension based on available evidence and consensus expert opinion." Superficially, the two groups appear to be engaged in the same endeavor, but a subtle distinction exists: whereas the NHLBI Working Group must provide a recommendation to accomplish its goal, the USPSTF need not. The balance of benefits and harms of pediatric BP screening may prove unknowable, or at least unprovable, in which case the USPSTF could (and does) satisfy its mission by saying so. The NHLBI Working Group, in contrast, must (and does) recommend whether or not to evaluate BPs in children and adolescents.

As mentioned, there are no clinical trials that directly link pediatric hypertension to increased mortality in either children or adults. Given the low mortality rate among pediatric patients, designing such a study would require following an enormous, stringently defined cohort for decades. Even if the logistics could be mastered

– no small feat – the results of this hypothetical study would not be available for a generation or more. In effect, then, each committee's recommendation turns upon the weight placed on the available indirect evidence, which will be considered in the next section.

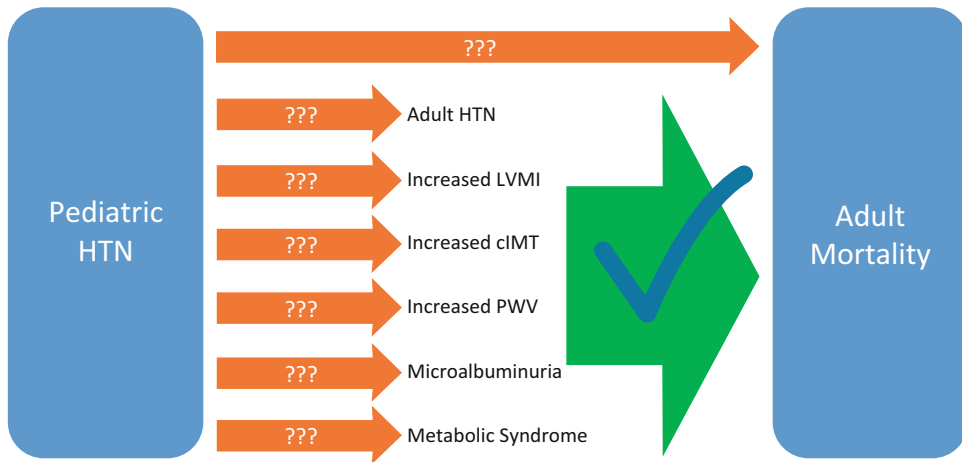
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## The Evidence Advocating Pediatric Hypertension as a Pathologic Condition

Because of the aforementioned difficulties in designing and conducting a study to analyze whether pediatric hypertension is associated with cardiovascular mortality, researchers have split this research question into more manageable components. The logic behind this rests on the premise that because adult hypertension is associated with mortality, if pediatric hypertension can be associated with adult hypertension, then pediatric hypertension becomes associated with mortality.

This concept of indirectly linking pediatric hypertension to adult mortality can also be seen in studies that analyze additional adult outcomes associated with mortality. These "intermediate outcomes" include left ventricular hypertrophy (LVH), increased carotid intima-media thickness (cIMT), abnormal arterial pulse wave velocity (PWV), microalbuminuria, and metabolic syndrome. Again, if pediatric hypertension can be associated with an adverse intermediate outcome, it becomes indirectly linked to cardiovascular mortality. These linkages are demonstrated in Fig. 1.

Splitting the question of whether pediatric hypertension is associated with mortality into two parts is beneficial in that the latter half of each question has already been answered: adult hypertension (Franklin and Wong 2013; Kung and Xu 2015; Sim et al. 2015), LVH (Levy et al. 1990; Verdecchia et al. 2001), increased cIMT (Den Ruijter et al. 2012), elevated PWV (Vlachopoulos et al. 2010), microalbuminuria (Gerstein et al. 2001; Hillege et al. 2002), and metabolic syndrome (Galassi et al. 2006; Gami et al. 2007) have all been associated with



**Fig. 1** Potential linkages between pediatric hypertension and adult cardiovascular mortality

increased cardiovascular mortality. However, determining whether pediatric hypertension is associated with any of the above still demands decades of follow-up. Fortunately, a partial answer can be glimpsed by examining the results of large, prospective cohort studies that have been established in several countries. Most of these studies began three to four decades ago, such that enough data has been collected on the earliest participants to begin elucidating the link between pediatric hypertension and adult outcomes. Indeed, all of the research discussed below is drawn from at least one of these cohort studies, which are summarized in Table 1.

The majority of the studies discussed below were considered by the NHLBI, the USPSTF, or both when crafting their recommendations, although more recent studies published after these reviews are also discussed here.

### Blood Pressure Tracking

In general, it appears that hypertensive children are more likely than non-hypertensive children to become hypertensive adults. Five studies involving members of Bogalusa Heart Study, Muscatine Study, Cardiovascular Risk in Young Finns Study, and Fels Longitudinal Study all demonstrate significantly increased risk ratios or odds ratios linking elevations in pediatric BP to

elevations in adult BP. The first of these was published by Beckett et al. (1992) and involved participants in the Fels Longitudinal Study. It focused on diastolic hypertension and found that 15-year-old males with diastolic BPs greater than 80 mmHg were three times more likely to have diastolic hypertension as adults. The effect was even more pronounced in 15-year-old females, who were four and a half times more likely to have diastolic hypertension as adults. Sun et al. (2007) used data from the Fels Longitudinal Study to look at the effects of systolic BP and found that increased systolic BP during childhood was significantly associated with adult hypertension in males aged 5–13 and in females aged 5–7 and 14–18. Males aged 14–18 and females aged 8–13 had odds ratios suggestive of an association, but these were not statistically significant.

Lauer et al. (1993) studied the Muscatine cohort and found that children with BPs greater than the 90th percentile were 2.4 times more likely to be hypertensive as adults when compared to children with normal BPs. Bao et al. (1995) studied the Bogalusa cohort and found a similar risk ratio of 3.6 when comparing children with BPs above the 80th percentile to those below the 80th percentile. Along the same lines, participants with elevated childhood BP in the Childhood Determinants of Adult Health Study had a 35% increased risk of developing adult hypertension compared to



**Table 1** Major prospective cohort studies investigating risk factors for cardiovascular disease from childhood into adulthood

Study	History	References
Cardiovascular Risk in Young Finns (Young Finns) (Finland)	Began in 1980 with the enrollment of 3,596 Finnish children and adolescents. Measurements taken at ages 3, 6, 9, 12, 15, and 18. Follow-up continues regularly	Raitakari et al. (2003), Juhola et al. (2011), and Aatola et al. (2014)
Bogalusa Heart Study (Bogalusa, LA, USA)	Began in 1973 and now has nine cross-sectional surveys of children aged 4–18 years in the study	Bao et al. (1995), Hoq et al. (2002), Li et al. (2003, 2004), and Lai et al. (2014),
Muscataine Study Adult Longitudinal Cohort (Muscatine, IA, USA)	Initial data collection took place between 1970 and 1981 and now has 865 adults with ongoing follow-up	Lauer et al. (1993), Burns et al. (2009), and Schubert et al. (2009)
Childhood Determinants of Adult Health (CDAH) (Australia)	Consists of 8,498 children aged 7–15 years were recruited in 1985. Blood pressures measured at 9, 12, and 15 years. Follow-up is ongoing	Juonala et al. (2010), Juhola et al. (2013), and Kelly et al. (2015)
Princeton Follow-up Study (Cincinnati, OH, USA)	The Princeton Lipid Control Study evaluated cardiovascular risk factors of 6775 children aged 6–18 between 1973 and 1976. From 1999 to 2003, follow-up of 1632 original participants was performed	Huang et al. (2008) and Schubert et al. (2009)
International Childhood Cardiovascular Cohort Consortium (i3C) (Multinational)	Formed in the mid-2000s from researchers involved with the five cohort studies described above, now includes several smaller cohort studies as well	Juonala et al. (2010) and Juhola et al. (2013)
Fels Longitudinal Study (Yellow Springs, OH, USA)	A longitudinal study that began in 1929 that annually examines participants. Recruitment continues today (and now includes great grandchildren of the original participants)	Beckett et al. (1992), Sun et al. (2007), and Schubert et al. (2009)

those with normal childhood BP (Kelly et al. 2015).

Only one study, however, looked at the positive predictive value of using pediatric hypertension to predict adult hypertension: that by Juhola et al. (2011), using the Cardiovascular Risk in Young Finns cohort. They obtained a PPV of 0.44, suggesting that about half of the participants who met criteria for hypertension as children continued to have hypertension as adults.

### Left Ventricular Hypertrophy

Only one study investigating the association between childhood BP and adult LVH has been conducted. Utilizing participants in the Bogalusa Heart Study, Lai et al. (2014) evaluated left ventricular hypertrophy in adults with at least two BP measurements obtained during childhood. They found that as childhood systolic BP

increased, the likelihood of adult LVH also increased, even when adjusting for other risk factors. This was a statistically significant finding, with an odds ratio of 1.27 (95% confidence interval 1.04–1.54).

### Carotid Intima-Media Thickness

Studies investigating the relationship between childhood BP and adult carotid IMT (cIMT) have demonstrated conflicting results, though the preponderance of evidence suggests that the two are linked. A study by Li et al. (2003), which included participants in the Bogalusa Heart Study, found no relationship between the two. That same year, however, a similar study by Raitakari et al. (2003) involving participants from the Cardiovascular Risk in Young Finns Study demonstrated a significant relationship between increasing systolic BP (measured when

participants were 12–18 years of age) and increasing cIMT.

More recently, two studies from the International Childhood Cardiac Cohort Consortium (i3C Consortium) have been conducted. These i3C Consortium studies combined data from the Young Finns Study, Bogalusa Heart Study, Muscatine Study Adult Longitudinal Cohort, and the Childhood Determinants of Adult Health Study and thus had more participants and greater power than the previous studies. Using this larger cohort, Juonala et al. (2010) found that, beginning at age 12, systolic BPs were significantly associated with increases in carotid IMT during adulthood. Juhola et al. (2013) then demonstrated that persistently elevated BP beginning at age 12 significantly increased carotid IMT in adulthood more so than elevated BP in adulthood alone. Interestingly, the researchers also found that elevated BPs in childhood that resolved by adulthood did not increase carotid IMT, suggesting that treatment of elevated BP in childhood may be effective at preventing end-organ damage.

### Arterial Pulse Wave Velocity

In an early study of arterial PWV, Li et al. (2004) evaluated the brachial-ankle PWV of adults in the Bogalusa Heart Study and found that increases in childhood systolic BP were significantly associated with increases in PWV. Unfortunately, further interpretation of this study is difficult because its results are presented in a confusing fashion: the authors provide beta coefficients from the regression model, but it is not clear what type of regression model was used and whether those coefficients are related to differences in means or odds ratios. However, the relationship between childhood BP and adult arterial PWV was strengthened when Aatola et al. (2014) investigated the PWV of participants originally aged 6–15 years in the Young Finns Study. They found that those participants with elevated BPs in childhood were 1.7 times more likely to have an elevated arterial PWV than those with normal BPs.

### Microalbuminuria

Hoq et al. (2002) investigated the relationship between microalbuminuria in adulthood and BP in childhood among participants in the Bogalusa Heart Study. Using a logistic regression accounting for other risk factors, they found a significant association between the two in African-Americans (with a p-value of 0.05), but not in whites (p-value of 0.776).

### Metabolic Syndrome

Using data from the Muscatine Study Adult Longitudinal Cohort, Burns et al. (2009) investigated risk factors for development of metabolic syndrome in 730 participants. They found that participants with childhood systolic BPs above the 75th percentile were 2.6 times as likely to develop metabolic syndrome as those participants with childhood systolic BPs below the 50th percentile. Huang et al. (2008) used data from the Princeton Follow-up Study to demonstrate that adults with metabolic syndrome had significantly higher systolic BP in childhood than those without metabolic syndrome. This finding was confirmed a later study by Schubert et al. (2009) using data from the Princeton Follow-up Study, Muscatine Study, and Fels Longitudinal Study.

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### Benefits of Screening

Though the evidence reviewed above is mixed, most studies suggest a connection between pediatric hypertension and worsening intermediate outcomes as adults. For the sake of argument, let us postulate that childhood hypertension and adult cardiovascular morbidity and mortality are causally linked. It stands to reason, then, that the diagnosis and treatment of hypertension – if safe and feasible – should be a priority during childhood.

The safety of BP screening (and, if necessary, resultant hypertension treatment) was thoroughly investigated by both the NHLBI and USPSTF. In this instance, both committees reached the same

conclusion: no significant harms were associated with BP screening, hypertension treatment via lifestyle changes, or hypertension treatment via medication. Safety, then, is not a concern. The only question remaining is whether treating pediatric hypertension prevents the development of cardiovascular morbidity and mortality.

Some evidence exists describing the beneficial effects of hypertension treatment during childhood and adolescence on many of the markers of cardiovascular disease delineated above. The best studied of these markers is LVH, and studies by Assadi (2007), Litwin et al. (2010), and Seeman et al. (2007) all have demonstrated improvements in left ventricular mass index (and therefore decreases in LVH) following hypertension treatment. Litwin et al. also demonstrated a reduction in the carotid IMT and the percentage of children qualifying for metabolic syndrome with hypertensive treatment. No such studies exist for the other intermediate outcomes, but it is certainly plausible that improved BP control would reduce arterial PWV and rates of microalbuminuria.

Aside from the controversy regarding screening for the prevention of long-term cardiovascular sequelae, screening children's BP remains beneficial in that this may lead to detection of significant underlying conditions that require specific treatment. In other words, hypertension in childhood may be secondary in origin, and screening BP measurements may lead to the early diagnosis of a causative problem. Two recent studies (Gupta-Malhotra et al. 2015; Flynn et al. 2012) have shown that over half of hypertensive children – particularly younger children – have secondary forms of hypertension. Sometimes, such as with coarctation of the aorta, renal artery stenosis, pheochromocytoma, or chronic kidney disease, hypertension is the major presenting symptom of this underlying condition. Thus, the diagnosis may go undiscovered if BPs are not routinely monitored. The morbidity associated with conditions causing secondary hypertension is clear but can potentially be reduced with early diagnosis and treatment. Routine BP screening goes a long way toward making that early diagnosis and treatment possible. Even if BP screening serves only to identify those patients with secondary hypertension – a big if,

considering the evidence above – it would seem to still be a worthwhile practice.

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## Future Directions

Overall, the cohort studies discussed above have made great progress in linking pediatric hypertension to intermediate outcomes that are themselves conclusively linked to adult cardiovascular disease and mortality. Most of these cohorts began in the 1970s and 1980s, and their usefulness has continued to grow over time. Assuming retention rates remain acceptable, the prevalence of studied outcomes should only increase. Additionally, cohort studies have begun to combine their participants (as evidenced by the i3C Consortium) which should greatly increase the power of future studies, providing data that could resolve the discrepancies noted above. With enough time and careful documentation, it may even be possible to directly investigate the association between pediatric hypertension and adult mortality. Though causation could not be proven given the study designs, a correlation between increasing childhood BP and adult cardiovascular mortality would be very suggestive.

The burgeoning use of electronic health records is also encouraging. Though much work remains to be done to improve EHR functionality, usability, and cross-platform compatibility, one can imagine a world in which the prospective cohorts discussed above are instead created retrospectively with a series of database queries. This world relies upon a number of assumptions, however: that the data in question exists (it has to be recorded to be stored in the database), that the data is of high quality, and that decades' worth of data is available for a given individual. As EHRs become more commonplace, researchers will have to work with informaticists and IT specialists to address these issues.

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## Conclusions

Pediatric hypertension is increasingly common, and its diagnosis requires diligence on the part of primary care providers. However, the consequences of undiagnosed pediatric hypertension are not entirely

clear. As such, expert committees differ widely in their recommendations as to whether or not children should have their BPs routinely monitored, with some proposing universal, annual screening and others suggesting no routine screening until age 18. The evidence linking pediatric hypertension to undesirable adult outcomes is also sometimes contradictory, and there is no direct evidence that elevated BP in childhood is problematic when those children become adults. However, there is mounting indirect evidence that hypertensive children are at greater risk for cardiovascular morbidity and mortality later in life. Furthermore, routine BP screening allows for the identification of secondary hypertension and the morbidity and mortality it represents. The continuance of multiple prospective cohort studies and the increasing use of electronic health records should provide more data and insight to hopefully resolve the question of whether or not to routinely perform pediatric BP screening.

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## Cross-References

- ▶ [Ambulatory Blood Pressure Monitoring Methodology and Norms in Children](#)
- ▶ [Development of Blood Pressure Norms and Definition of Hypertension in Children](#)
- ▶ [Methodology of Casual Blood Pressure Measurement](#)

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# Development of Blood Pressure Norms and Definition of Hypertension in Children

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Bonita Falkner

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## Abstract

The definition of hypertension in children and adolescents is based on blood pressure data from a large population of healthy children and adolescents from infancy to age 17 years. Such data were not available prior to the 1970s, and measurement of blood pressure was not a standard practice in asymptomatic healthy children at the time. In the absence of reference data on blood pressure levels in healthy children, adult criteria were used. Early preliminary data on blood pressure levels in healthy children indicated that the normal range of blood pressure was considerably lower than in adults, and there was a progressive increase in blood pressure levels that corresponded to childhood growth and development. Subsequently, several large observational studies were conducted on healthy children and adolescents. These studies applied uniform methods in blood pressure measurement along with growth measures of height and weight. The combined data from these studies were analyzed to determine the normal childhood distribution of blood pressure levels upon which current childhood definitions of hypertension are based. In the absence of morbidity and mortality data, hypertension in

childhood is defined statistically based upon the distribution of blood pressure values in otherwise healthy children.

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## Keywords

Blood pressure • Hypertension • Prehypertension • Children • Adolescents • Growth

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## Introduction

Assessment of blood pressure in children and adolescents, as a measure of health status, is now part of routine clinical practice. Prior to the 1970s, blood pressure was not commonly measured in very young children due to the difficulty in obtaining reliable measurements and the general belief that hypertension was a rare problem in

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children (McCory and Nash 1952). Since measurement of blood pressure had not yet become routine, high blood pressure was detected only when significant clinical signs or symptoms were present. In the absence of any childhood blood pressure data on which to base an age-appropriate definition of hypertension, adult criteria were the only available reference information. Based on our current knowledge about normal blood pressure in healthy children, we now know that the early descriptions of hypertension in the young represented only the most severe cases of childhood hypertension.

The development of developmentally appropriate normal values for childhood blood pressure has led to a significant shift in our understanding of hypertension in the young. Prior to 1970, it was widely believed that hypertension in children was always secondary to an underlying cause, and primary, or essential, hypertension did not exist in the young. With the development and understanding of reference data on blood pressure in the young, relative to childhood growth and development, this belief has changed. There is now a substantial body of blood pressure data and clinical experience that enable clinicians to evaluate the blood pressure level in a given child relative to age, sex, body size, and other clinical parameters. Moreover, the clinician can use the available reference blood pressure data and the clinical characteristics of the child to determine the child's health status in terms of health, having risk factors that warrant preventive intervention, or having a blood pressure level that necessitates further evaluation. Some children, especially younger children, do indeed have hypertension secondary to an underlying disorder such as renal disease, endocrine disorders, or cardiac and vascular abnormalities. It is now also known that essential (primary) hypertension can be detected in the young. An important value of recognizing the early phase of essential hypertension is the potential ability to modify subsequent outcomes in adverse cardiovascular events.

The advancement in knowledge on childhood hypertension over the past 40 years has developed from a process of accumulating, evaluating,

and understanding data on blood pressure levels in children and adolescents. The outcome of this process is the blood pressure normative data on which the current definitions of normal and abnormal blood pressure levels in childhood are based. Blood pressure is a measurement of a circulatory parameter which at higher levels is a well-described risk factor for future cardiovascular events. Blood pressure may also be indicative of a disease, either secondary to an underlying disorder or primary hypertension. Today, the definitions of hypertension in childhood are based on the normative blood pressure data generated from over 60,000 children. This chapter will discuss the evolution of the blood pressure normative data in childhood and their use in detection, evaluation, and management of hypertension in childhood.

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## Outcome of Childhood Hypertension

Hypertension is a significant health problem to the extent that adverse clinical outcomes can be attributed to or associated with blood pressure levels that exceed a certain level. Prior to a publication in 1967 by Still and Cottom (Still and Cottom 1967), little was known about the health consequences of hypertension in childhood. These authors provided one of the first descriptions on the outcome of severe hypertension in children by reviewing cases of children with sustained diastolic blood pressure greater than 120 mmHg treated at the Hospital for Sick Children Great Ormond Street from 1954 to 1964. Of the 55 cases reviewed, 31 died, 18 survived with treatment that achieved a reduction in blood pressure, and 6 were cured of the hypertension following corrective surgery for an identifiable lesion (coarctation repair, unilateral nephrectomy, pheochromocytoma removal). Of the cases that died, the average duration of survival following diagnosis of the hypertension was only 14 months. In this early case review, the sample of children with severe uncontrolled hypertension had a mortality rate of 90% in slightly over 1 year, a mortality rate that is the same as that of malignant hypertension in adults.



While these numbers are shocking by today's standards, the message made at that time was that severe hypertension in a child could be as deadly as it was in an adult.

The above report and others of that period were limited to children with what would now be considered very severe hypertension. In the absence of blood pressure data on normal children, the conventional adult cut point of 140/90 mmHg was generally used to define hypertension in children. This practice limited the diagnosis of hypertension in children to those with the most extreme elevations of blood pressure. In children, severe hypertension is frequently associated with renal disease or some other disorder that causes the hypertension. As a result, for some time the focus of childhood hypertension was on the evaluation for underlying disease and search for a secondary cause. Subsequent efforts to develop normative data on blood pressure in childhood were a necessary prelude for a shift from the narrow focus of secondary hypertension to a broader perspective that high levels of blood pressure could indicate an early phase of a chronic process. It was established that severe hypertension had an adverse outcome if left untreated. What was yet to be determined was how frequently did hypertension occur, and what level of blood pressure elevation in a given child conferred risk for target organ or vessel injury.

## Prevalence of Hypertension in Childhood

In the last half of the twentieth century, hypertension was established as a significant health problem in adults, and efforts were underway, from both a public health and clinical care perspective, to improve detection and management of hypertension. To a large extent, hypertension was regarded as a component of aging and a reflection of chronic atherosclerosis. Thus, hypertension appeared to have little relevance in the young. Jennifer Loggie was one of the first to consider the possibility that "essential" hypertension could be detected in adolescents. In a review article (Loggie 1974), Loggie discussed the available reports at that time on the prevalence of hypertension in persons 25 years or less. Of the five published reports (Masland et al. 1956; Boe et al. 1957; Heyden et al. 1969; Londe 1966; Wilber et al. 1972) that attempted to determine the prevalence of hypertension in the young by conducting blood pressure screening on large samples of healthy individuals, the rates of hypertension ranged from 1% to 12.4%. Table 1 summarizes these reports and denotes the differences in the criteria used to define hypertension, methods of measurement (sitting vs. supine), and the age of the sample examined. The majority of these early reports on hypertension in adolescents and young adults defined hypertension according

**Table 1** Reported prevalence of hypertension in persons 25 years of age or less prior to normative data

Authors	Subjects age (yr)	Number screened	Position in which pressure was taken	Definition of hypertension (mmHg)	Prevalence (%)
Masland et al. (1956)	"Adolescents"	1795	Not stated	140/90	1.4
Boe et al. (1957)	15–19	3833	Sitting	150/90	3.01 Males 1.04 Females
Heyden et al. (1969)	15–25	435	Sitting	140/90	11.0
Londe (1966)	4–15	1473	Supine	Systolic or diastolic >90th <sup>%</sup>	12.4 Males 11.6 Females
				Systolic or diastolic >95th% (Repeated measures)	1.9
Wilber et al. (1972)	15–25	799	Sitting	Systolic >160	1.0
				Diastolic >90	1.5

to a blood pressure level that was similar to values used for adults. However, the report by Londe (Londe 1966) which examined younger children, age 4–15 years, used a different definition of hypertension. Londe had measured blood pressure on children in his own pediatric clinic and observed that blood pressure levels rise with age, concurrent with growth and development. He then analyzed the blood pressure data to determine the range of systolic and diastolic blood pressure stratified by age and selected the 90th percentile for each age that defined hypertension. Thus, his reported rates of hypertension were consistent with his definition and were slightly above 10%. He also noted that on repeated measurement, there was regression toward the mean, and the prevalence of persistent systolic or diastolic blood pressure greater than the 95th percentile was 1.9%. Little attention was given to Londe's work for some time. However, it is remarkable that that number of 1.9% of children with systolic or diastolic blood pressure equal to or greater than the 95th percentile on repeated measurement is close to more contemporary estimates of pediatric hypertension derived from far larger numbers of children.

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### **Definition of Hypertension in Childhood**

The fundamental problem to be resolved was what constituted normal blood pressure and what level of blood pressure defined hypertension in the young. In adults, the definition of hypertension is based on the approximate level of blood pressure that marks an above average increase in mortality. The cut-point numbers for abnormal blood pressure level were largely based on actuarial data from life insurance mortality investigations that indicated an increase in death rates occurred when the systolic blood pressure exceeded 140 mmHg or the diastolic blood pressure exceeded 90 mmHg.

This method to define hypertension was challenged by Master et al. (Master et al. 1950) in a report published in 1950. These authors argued that defining hypertension by a single number was

arbitrary, because hypertension occurred far more frequently in the elderly and was commonly associated with atherosclerosis. They contended that an increase in blood pressure was a reflection of aging, and that the use of one number to define a disorder for all ages resulted in an overdiagnosis of hypertension in the elderly. They proposed a statistical definition based on the distribution of blood pressure readings around the mean, according to sex and age. Blood pressure, like most human characteristics, demonstrates a frequency distribution that yields a fairly normal curve. In a normal distribution, roughly two thirds of the observations will occur within the range of the statistical mean plus or minus one standard deviation from the mean, and 95% of the observations will be within the range of the mean plus or minus two standard deviations. They proposed that blood pressure that reached a level that was two standard deviations beyond the statistical mean, or greater than the 95th percentile, should be considered abnormal. Master et al. supported their position by examining data obtained from industrial plants in various sections of the country on about 7400 persons who were considered to be in "average good health and able to work." Using a statistical method to define the normal range of blood pressure, they described the normal range of systolic blood pressure in males to be 105–135 mmHg at 16 years of age and rising progressively with age to reach 115–170 mmHg at age 60–64 years. They also noted a gender difference in the normal range. Females had a normal range of systolic blood pressure of 100–130 mmHg at 16 years of age, and at 60–64 years of age the normal range was 115–175 mmHg. The conclusion of these authors was that hypertension was overdiagnosed in adults, particularly in the elderly. Their conclusion was supported, they believed, by demonstrating that large numbers of persons with blood pressure above 140/90 mmHg were living with blood pressure at that level and were "in average good health and able to work."

A large body of subsequent epidemiological and clinical investigations on hypertension in adults has clearly dismissed the conclusion by Master et al. that hypertension is overdiagnosed

because the normal range of blood pressure increases with age. Several expert panels define hypertension in adults according to the level of blood pressure that marks an increase in cardiovascular events and mortality. This definition, for some time, has been systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg (Joint National Committee 1997). These numbers are approximate blood pressure levels above which the risk for morbid events is significantly heightened and the benefits of treatment are established. It is also now recognized that the risk for cardiovascular events attributable to blood pressure level in adults does not begin only at 140/90 mmHg, but the risk is linear and begins to rise starting at lower levels of blood pressure. Data derived from the Framingham Study in adults show that blood pressure in the range of 130/85 to 139/89 mmHg confers more than double the absolute risk for total cardiovascular events following 10 years, compared to blood pressure  $< 120/80$  mmHg (Vasan et al. 2001). In response to this emerging epidemiological data, the concept of prehypertension was developed to designate a blood pressure range wherein adults could benefit from preventive lifestyle changes (Chobanian et al. 2003). More recent clinical trials in adults with diabetes, chronic kidney disease, and older adults at high risk for cardiovascular events have developed evidence that support recommendations to treat and achieve blood pressure levels lower than 140/90 mmHg. As yet, there are no comparable data that provide a direct link between a level of blood pressure in childhood and morbid events at some time later in adulthood. The original report by Masters et al. is the earliest to show that the normal range of blood pressure is lower at age 16–19 years than in older adults. Of most significance is that Masters et al. provided a statistical method to define the normal blood pressure range, and abnormal blood pressure could then be defined in the absence of mortality or morbidity end points.

Until the early 1970s, the prevalence of hypertension in children and adolescence was largely unknown. Accurately describing the prevalence of hypertension in the young,

however, could not be done without a uniform and consistent definition of hypertension in this population. Moreover, this definition of hypertension could not be developed in the absence of knowledge about what constituted normal blood pressure in children and adolescents. There were some, but quite limited, data on blood pressure levels in asymptomatic healthy children. The available data indicated that the level of blood pressure was considerably lower in young children than in adults, and that there appeared to be a normal rise in blood pressure with age that was concurrent with growth. It was also recognized that due to differences in measurement techniques, there was likely to be considerable variability in the child blood pressure data that was available.

Initial efforts to gain a better understanding of the prevalence of hypertension in the young focused on adolescents. Based on a careful examination of her own clinical data derived from children and adolescents that she had evaluated for blood pressure elevation, Loggie (Loggie 1974) suggested that essential hypertension was more common in adolescents than had been previously believed. Kilcoyne et al. (Kilcoyne et al. 1974) made an effort to determine if asymptomatic hypertension could be detected in otherwise healthy adolescents. These investigators conducted blood pressure screening on urban high school students. They observed that female students of all races had lower levels of systolic blood pressure than males. Using 140/90 mmHg as a definition of hypertension, they detected an overall prevalence of 5.4% systolic and 7.8% diastolic hypertension at the initial screening; follow-up screening on those with elevated measurements demonstrated a decline in prevalence to 1.2% systolic and 2.4% diastolic hypertension. They also noted higher rates of sustained hypertension among the Black males. These investigators examined their data further by creating frequency distributions of systolic blood pressures in the males at successive age levels of 14, 16, and 18 years. These distribution curves demonstrated a progressive rightward displacement with increasing age, which, the authors suggested, indicated a transition to adult

characteristics. However, they also noted that this shift in distribution did not occur in females between 14 and 19 years of age. Based on these data, these investigators suggested that the criteria used to define hypertension in adolescents would be more meaningful if they were based on the frequency distributions of blood pressure levels in an adolescent sample. They proposed that values exceeding one standard deviation above the statistical mean would more appropriately define hypertension. From their data, one standard deviation above the mean would be 132/85 mmHg for males and 123/82 mmHg for females. It is of note that, although one and not two standard deviations above the mean were proposed, these values are reasonably close to the numbers that Master et al. (Master et al. 1950) reported to be at the top of the normal range for persons 16–19 years of age (males 135 mmHg; females 130 mmHg).

Similar early efforts to investigate blood pressure levels and the prevalence of hypertension in healthy adolescents were conducted by other investigators, largely in the context of high school screening projects (Kotchen et al. 1974), (Miller and Shekelle 1976), (Garbus et al. 1980). From these studies, the investigators detected initial rates of hypertension, when adult criteria were used, at approximately 5%. This rate decreased with repeat blood pressure measurement. These reports also noted lower blood pressure levels in adolescent females compared to males. Some difference in blood pressure by race was reported, with higher levels of blood pressure and more hypertension among African Americans. An effect of weight on blood pressure was also described. Together these reports emphasized a need to develop a better definition of hypertension in the young, a definition that would be based on reference data derived from a large sample of healthy children.

The National Heart, Lung, and Blood Institute (NHLBI) recognized the gaps in understanding the normal distribution of blood pressure levels and hypertension in childhood and directed the National High Blood Pressure Education Program to appoint a Task Force on Blood Pressure Control in Children in the mid-1970s. This Task Force

published its first report in 1977 (Task Force 1977). The Task Force goals were to: (1) describe a standard methodology for measurement of blood pressure in the young; (2) provide blood pressure distribution curves by age and sex; (3) recommend a blood pressure level that is the upper limit of normal; and (4) provide guidelines for detection, evaluation, and treatment of children with elevated blood pressure. The blood pressure distribution curves in this report were based on data gathered from three observational studies conducted in Muscatine, Iowa; Rochester, Minnesota; and Miami, Florida. The total size of the sample was 9283 children from age 5 through 18 years, with an additional 306 children age 2–5 years (Miami). The blood pressure data were presented as percentile curves, by age, for systolic and diastolic blood pressure in males and females, similar to the standard pediatric growth curves for weight and height.

These blood pressure curves represented a substantial advancement in our understanding of blood pressure levels in the young, particularly for clinicians who care for children. Although based on cross-sectional data, the curves indicated a progressive increase in blood pressure level with age, a trend that is concurrent with increasing height and weight. The blood pressure curves also established a normative range for blood pressure in early childhood that was different than that of adults. Using a statistical definition, the recommended definition of hypertension was a blood pressure level that is equal to or greater than the 95th percentile for age and sex, if verified on repeated measurement. These blood pressure curves, for the first time, provided a clear view on the levels of blood pressure that were outside of the normal range in young children. However, by age 13 years in boys the 95th percentile had reached 140 mmHg and 90 mmHg for systolic and diastolic pressure, respectively, with a progressive rise to 18 years, at which age the 95th percentile was over 150 mmHg systolic and 95 mmHg diastolic. These numbers seemed to indicate that by early adolescence the adult criteria to define hypertension would be appropriate. However, the 95th percentile delineated blood pressure levels provided in this report seemed to be high for older adolescents when compared to the data that had been collected

in the preceding high school screening studies. This discrepancy raised concern as to how well these distribution curves truly reflected the normative blood pressure distribution in healthy children and adolescents.

## Normative Blood Pressure Distribution in Children and Adolescents

The first Task Force on Blood Pressure Control in Children and Adolescents established the importance of blood pressure levels in childhood as an indicator of health status (Task Force 1977). It provided a standard methodology for measurement of blood pressure in children and encouraged clinicians to measure blood pressure in the young. It also provided a definition of hypertension that could be applied to children. However, whether the blood pressure curves published in the report were an accurate reflection of the normative blood pressure distribution in healthy children remained in question. The NHLBI recognized the need to obtain a larger body of data on blood pressure levels in the young within the context of childhood growth, and subsequently supported several epidemiological studies that prospectively investigated blood pressure levels and blood pressure trends as they relate to growth in children and adolescents. These projects were conducted at several sites, applied rigorous detail to the methodology of blood pressure measurement, and examined the anthropometric determinants of blood pressure levels relative to physiological development.

As these data emerged, a second Task Force on Blood Pressure Control in Children and Adolescents was convened to reexamine the data on blood pressure distribution throughout childhood and prepare distribution curves of blood pressure by age accompanied by height and weight information. With this new information, the second Task Force also updated the guidelines for detection, evaluation, and management of hypertension in the young in its 1987 report (Task Force 1987). Table 2 provides the sites that contributed data that was used to develop the new blood pressure distribution curves. The total number of children on whom blood pressure data were available was over 60,000. This sample included an age range from infancy to age 20 years with a substantial representation of different race and ethnic groups. The blood pressure percentile curves published in the Second Task Force Report again demonstrated a progressive rise in blood pressure that was concurrent with age. Gender differences in blood pressure levels during adolescence were verified. The blood pressure levels in males continued to increase from age 13 through 18 years, whereas the blood pressure levels in females tended to plateau after age 13 years, and the normal distribution was somewhat higher in adolescent males compared to females. Moreover, the entire distribution was lower and consequently the 95th percentile delineated a level of blood pressure that was substantially lower than that described in the previous report.

The Second Task Force Report applied the same definition of hypertension that was used in the first Task Force Report, which was systolic or

**Table 2** Data sources for The Second Task Force Report

Source	Age (yr)	N
Muscataine, IA	5–19	4208
University of South Carolina	4–20	6657
University of Texas, Houston	3–17	2922
Bogalusa, LA	1–20	16,442
Second National Health and Nutrition Examination Survey	6–20	4563
University of Texas, Dallas	13–19	24,792
University of Pittsburgh	Newborn-5	1554
Providence, RI	Newborn-3	3487
Brompton, England	Newborn-3	7804

diastolic blood pressure that was repeatedly equal to or greater than the 95th percentile. However, in consideration of how much lower the 95th percentile appeared to be at that time, along with the concern about possibly overdiagnosing hypertension in the young, this report included a classification table for “*significant*” and “*severe*” hypertension. According to age strata, blood pressure values that fell between the 95 and 99th percentiles were designated significant hypertension, and blood pressure values that exceeded the 99th percentile were designated severe hypertension. At the time that report was developed, it could seem that the authors were hedging on the definition of hypertension in the young. However, by intention or not, the concept of staging hypertension on the basis of degree of blood pressure elevation was novel and had not yet been considered in the field of adult hypertension. It was not until the publication of the 6th Report of the Joint National Commission in 1997 (Joint National Committee 1997) that hypertension stage was introduced as a method to guide patient care and clinical management decisions in adults.

Subsequent to the 1987 Task Force Report, additional childhood blood pressure data were developed from the National Health and Nutrition Examination Survey (NHANES) III reports (Centers for Disease Control 1991). Other reports were also published on data indicating that children with elevated blood pressure in childhood often developed hypertension in early adulthood (Lauer and Clarke 1989). Based on increasing support for the concept that the origins of hypertension begin in the young, rationale was developing for an emphasis on blood pressure surveillance in childhood, along with early preventive efforts. A reexamination of the national data on childhood blood pressure was necessary to provide substance to such recommendations. Therefore, a third Task Force was convened to update the normative data as well as the guidelines for management to include increased attention on preventive guidelines.

The addition of the new blood pressure data and reanalysis of the entire childhood data base resulted in blood pressure distribution curves that were slightly lower, but generally consistent with

the findings of the second Task Force. The third report (National High Blood Pressure Education Program and Working Group on Hypertension Control in Children and Adolescents 1996), which was termed “Update on the 1987 Task Force Report,” provided further detail on the relationship of body size to blood pressure. The contribution of body size had been considered in the analysis that was conducted by the Second Task Force, as well as the analyses of the data from individual sites by the investigators who had developed the data. Analysis of that data indicated that height and body weight, as well as age, were major determinants of blood pressure level. Height was considered to be the best determinant of blood pressure that was within the normal range. Therefore, it was recommended that height adjustment be applied in the evaluation of blood pressure level. To support this practice, the Second Task Force Report contained information on the 90th height percentile at the 90th percentile for blood pressure. It was assumed that pediatricians, who were accustomed to making weight for height adjustments, would be able to make the blood pressure adjustment for height. The third “Update” report expanded the presentation of the data by providing tables with the 90th and 95th percentile levels of systolic and diastolic blood pressure for multiple height percentiles (5th, 10th, 25th, 50th, 75th, 90th, and 95th) by age (1–17 years). These tables provided a better view on the normal variation of blood pressure that occurs with increasing height and age.

The childhood blood pressure data was reexamined by a fourth Working Group (Fourth Report) that published expanded blood pressure percentile tables in 2004 (Falkner et al. 2004). These tables provide the sex, age, and height blood pressure levels for the 50th and 99th percentile as well as the 90th and 95th percentile. The intent of the Fourth Report was to provide additional guidelines in the detection and clinical management of childhood hypertension. The definition of hypertension in childhood remains the same; systolic and/or diastolic blood pressure  $\geq$  95th percentile was verified on repeated measurement. The Fourth Report provided additional precision in the staging of hypertension. Stage

1 hypertension was defined as systolic or diastolic blood pressure between the 95th percentile and 5 mm Hg above the 99th percentile. Stage 2 hypertension is defined as systolic or diastolic blood pressure that is greater than the 99th percentile plus 5 mmHg. The category of “high normal blood pressure” was replaced with a stage termed “prehypertension.” Prehypertension was defined as systolic and/or diastolic blood pressure  $\geq$  90th percentile and  $<$  95th percentile. At that time, the definition of prehypertension in adults was systolic blood pressure between 120–139 mmHg or diastolic blood pressure between 80–89 mmHg (Chobanian et al. 2003). Beginning at age 12 years, the 90th percentile is higher than 120/80 mmHg, with the exception of very short young adolescents. Therefore, to be consistent with the adult definition of prehypertension, prehypertension in adolescents was defined as blood pressure from 120/80 mmHg to  $<$  95th percentile. In this report, additional guidelines were provided for evaluation and treatment of abnormal blood pressure according to these defined stages, and recommendations were made for evaluating other cardiovascular risk factors and target organ damage related to high blood pressure. A similar approach to defining hypertension was adopted in the 2017 American Academy of Pediatrics (AAP) childhood hypertension guideline, as summarized in the Appendix.

Following publication of the Fourth Report, subsequent publications have reported data on the prevalence of hypertension based on its definitions. Hansen et al. (2007) applied the above criteria for hypertension and prehypertension to electronic medical record data from well-child care visits in a cohort of over 14,000 primary care patients. With the advantage of data on repeat blood pressure measurements on separate visits, these investigators determined the prevalence of hypertension to be 3.6% and the prevalence of prehypertension to be 3.4% in children and adolescents between the age of 3 and 18 years. In a cross-sectional study limited to the adolescent age, the prevalence of prehypertension and hypertension was determined in a cohort of 6790 high school students (11–17 years). Using the recommended repeated blood pressure measurements on those with an

elevated initial blood pressure measurement, the prevalence of hypertension was 3.2% and the prevalence of prehypertension was 15.7% (McNiece et al. 2007). In both reports the presence of obesity was associated with higher rates of high blood pressure. In the study on high school students by McNiece et al. (2007), the prevalence of hypertension and prehypertension combined was over 30% in obese boys and from 23% to 30% in obese girls depending on ethnicity.

A childhood obesity epidemic was clearly established prior to the Fourth Report in 2004. The association of overweight and obesity with higher blood pressure has been consistently demonstrated in children (Hansen et al. 2007) (McNiece et al. 2007) (Ogden et al. 2002) as well as adults. The effect of the increase in childhood obesity on blood pressure was demonstrated by Muntner et al. (Munter et al. 2004) who compared blood pressure levels in children on data in two sequential NHANES periods. Their analysis identified a significant upward trend in blood pressure levels in children and adolescents. The authors determined that the increase in blood pressure level was largely, but not entirely, attributable to the increase in body mass index. The blood pressure increase was most striking among minority groups that also had the highest rates of childhood obesity. Another analysis on the same two data cohorts demonstrated an overall increase in the prevalence of hypertension from 2.7% in the 1988–1994 survey to 3.7% in the 1999–2002 survey period (Din-Dzietham et al. 2007). Both analyses concurred that the population increase in blood pressure level and rates of hypertension among children and adolescents were largely due to the increase in prevalence and severity of childhood obesity. The blood pressure percentile tables provided in the Fourth Report (2004) are based on child population data mostly developed prior to the child obesity epidemic. To determine if there is a substantial effect of obesity on those normative data, Rosner et al. (Rosner et al. 2008) reexamined the childhood blood pressure normative data by including only normal weight children (BMI  $<$ 85th percentile). Their analysis of blood pressure data, limited to normal weight children and adolescents, demonstrated somewhat lower

blood pressure thresholds for the 90th and 95th percentiles when compared to the blood pressure levels published in the Fourth Report.

Although the blood pressure levels in the tables are not markedly lower, the tables developed by Rosner et al. (2008) along with the known adverse effect of obesity on blood pressure in childhood raise the question of whether the normative blood pressure data should be based on normal weight children only. In fact, this approach was adopted by the AAP in development of its 2017 childhood hypertension guideline, resulting in generation of new normative blood pressure tables. These are provided in the Appendix to this text.

The BP data used to generate the normative tables found in the Fourth Report and the new 2017 AAP guideline have been collected according to rigorous and quite uniform measurement methodology. The population sample from which the data was obtained represents diverse race and ethnic groups from several areas of the United States. The analysis of these data and development of blood pressure norms provide a framework upon which to identify children and adolescents with hypertension and also to ascertain risk for future hypertension. Blood pressure reference values have also been reported in Northern Europe (Munkhaugen et al. 2008) and Asia (Sung et al. 2008). These reports describe a slightly higher blood pressure level at the 95th percentile compared to the US data. However, all epidemiological reports on normative childhood blood pressure data demonstrate a consistent and significant relationship of blood pressure with sex, age, height, and body weight throughout childhood.

### **Application of Blood Pressure Normative Data**

The quality of contemporary blood pressure normative data has improved compared to that provided in the first Task Force report published in 1977. This is largely due to application of a consistent methodology in blood pressure measurement. Changes in

clinical practice methods need to be considered when using the normative blood pressure tables. The normative blood pressure data published in the Fourth Report (2004), as well as the previous reports sponsored by the National High Blood Pressure Education Program, are based on blood pressure measurements obtained by auscultation. In clinical practice there has been increasing reliance on automated blood pressure instruments to measure blood pressure in children as well as adults. Blood pressure measured with these devices will vary from blood pressure measured by auscultation. There is also measurement variation between automated devices developed by different companies. It is very unlikely that child population blood pressure data of similar magnitude will ever be developed on each of the available automated devices. Therefore, in clinical practice, the automated instruments should be limited to screening and auscultation should be used for verification of an elevated blood pressure.

Other blood pressure databases have been developed which, out of necessity, have utilized instrumentation for blood pressure measurement other than auscultation. Blood pressure monitoring with oscillometric devices are used as standard care in neonatal care units. These devices have enabled the collection of a sufficient body of blood pressure data to develop a normative blood pressure range in both normal weight and low birth weight infants (Zubrow et al. 1995; Pejovic et al. 2007). Although the magnitude of the normative data in newborn infants remains limited, the available data demonstrate a consistent association of blood pressure with body size and gestational age and also provide a reference on which to identify and manage neonatal hypertension.

Given the nature of the procedure, ambulatory blood pressure monitoring (ABPM) also requires automated blood pressure instrumentations. In addition to applications for clinical research, ABPM has become a useful tool in the clinical evaluation of high blood pressure in children and adolescents, as well as in adults (Urbina et al. 2008; Flynn et al. 2014). The development of normative



childhood data using ABPM is especially challenging from both a data collection and data analysis standpoint. Despite these difficulties, some normative ABPM data in children, with sex and age (or height) adjusted percentiles, are available (Wuhl et al. 2002). Reference blood pressure levels at the 50th, 75th, 90th, 95th, and 99th percentile have been developed for 24-h average systolic and diastolic blood pressure. In addition, similar reference values are available for both wake and sleep periods. These ABPM normative datatables are provided for each gender by either age or height (measured in centimeters rather than height percentile). One limitation of the available ABPM data is that the population on which it was obtained was entirely Caucasian without representation of other racial groups. Additionally, the number of children included in this dataset (n=949) is quite small in comparison to the number of children involved in developing the normal values for casual blood pressure.

In the absence of outcome data that connect a specific childhood blood pressure level with subsequent injury or events, the definition of hypertension in childhood continues to be statistically derived from normative data. Therefore a systolic or diastolic blood pressure greater than or equal to the 95th percentile for age, sex, and height remains a working definition of hypertension in childhood. However, evidence that the 95th percentile adequately represents the risk for hypertension-related organ and vascular injury remains limited, and research to describe the long-term outcomes associated with this definition is greatly needed.

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## Conclusion

Overall the body of normative blood pressure data, obtained by auscultation, in children and adolescents from age 1 to 17 years has remained fairly stable since the 1987 Task Force Report. Because it largely precedes the child obesity epidemic, these data provide a basis on which to detect trends in

blood pressure level and the prevalence of hypertension in children. The Fourth Report normative blood pressure tables, although based on a large representative child population and rigorous blood pressure methodology, do have some limitations in their clinical use. The tables are intentionally precise with blood pressure values according to sex, age, and height percentile to minimize over- or underdiagnosis of hypertension. Consequently, the tables are complex and cumbersome to use in clinical practice. Thus, even though blood pressure measurement has become well integrated into routine pediatric care, abnormal blood pressure levels are frequently not recognized (Hansen et al. 2007; Brady et al. 2010). Simplified blood pressure tables have been developed and proposed as a tool to prompt clinicians on when to repeat the blood pressure measurement and consult the Fourth Report tables (Kaebler and Pickett 2009). Based on the known adverse effect of overweight and obesity on blood pressure levels, the 2017 AAP childhood hypertension guideline includes revised normative blood pressure tables that are based only on healthy weight children and adolescents. The 2017 guideline also includes a simplified table to be used as a screening tool to facilitate recognition of elevated blood pressure and to prompt repeat blood pressure measurement. Finally, research connecting the current epidemiologically based definition for hypertension in children with long-term cardiovascular outcomes (or earlier subclinical changes) is needed to ensure that all children at risk are appropriately identified and treated.

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## Cross-References

- ▶ [Ambulatory Blood Pressure Monitoring Methodology and Norms in Children](#)
- ▶ [Epidemiology of Cardiovascular Disease in Children](#)
- ▶ [Epidemiology of Primary Hypertension in Children](#)
- ▶ [Methodology of Casual Blood Pressure Measurement](#)
- ▶ [Neonatal and Infant Hypertension](#)

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# Ambulatory Blood Pressure Monitoring Methodology and Norms in Children

Elke Wühl

## Abstract

Over the last decades, ambulatory blood pressure monitoring (ABPM) has become a method of choice for the diagnosis and therapeutic monitoring of arterial hypertension in adult and pediatric patients. ABPM allows a more representative observation of blood pressure throughout day and night in a nonmedical environment compared to office blood pressure measurements as well as assessment of the circadian and even ultradian blood pressure variability. ABPM provides ability to detect white coat and masked hypertension, a better reproducibility of measurements and superior prediction of target organ damage. The use, interpretation, and limitations of ABPM in children and adolescents will be discussed in this chapter.

## Keywords

Hypertension • Ambulatory blood pressure monitoring • Children • Pediatrics • White coat hypertension • Masked hypertension

## Abbreviations

ABPM Ambulatory blood pressure monitoring  
BP Blood pressure

CKD Chronic kidney disease  
CV Cardiovascular  
CVD Cardiovascular disease  
DBP Diastolic blood pressure  
HTN Hypertension  
MAP Mean arterial blood pressure  
MH Masked hypertension  
OBP Office (or casual) blood pressure measurement  
SBP Systolic blood pressure  
TOD Target organ damage  
WCH White coat hypertension

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## Introduction

The prevalence of elevated blood pressure and hypertension in children seems to be increasing in parallel to the growing prevalence of overweight and obesity in the USA and in Europe (Din-Dzietham et al. 2007; Rosner et al. 2013; Flechtner-Mors et al. 2015). In view of the evolving influence of pediatric hypertension on cardiovascular risk (Tracy et al. 1995; Homma et al. 2001; Li et al. 2004; Juonala et al. 2010; Koivisto et al. 2011), precise and timely identification of hypertension is recommended (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004; Lurbe et al. 2016; Flynn et al. 2017). While there is substantial evidence that ambulatory blood pressure monitoring (ABPM) may be superior to office blood pressure measurements (OBP) in predicting cardiovascular (CV) morbidity and mortality in adults (Perloff et al. 1989; White et al. 1989b; Staessen et al. 1999; Cuspidi et al. 2001), clinical endpoint assessment in patients with childhood onset hypertension is still lacking. However, there is emerging evidence for a superior association between ambulatory blood pressure and preclinical target organ damage (TOD) in youths, with left ventricular hypertrophy (LVH), assessed by echocardiography, being the most studied index (Kollias et al. 2014).

Furthermore, ABPM allows a more representative observation of blood pressure (BP) throughout day and night in a nonmedical environment, detailed assessment of the circadian and even ultradian blood pressure variability, detection of white coat hypertension (WCH) and masked hypertension (MH) and eliminates observer bias. Thus, ABPM is increasingly used in the diagnosis of hypertension and evaluation of target organ damage in both children and adults.

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## Advantages of Ambulatory Blood Pressure Monitoring

### Role of Ambulatory Blood Pressure Monitoring in the Diagnosis of Specific Conditions

ABPM is a stronger predictor of cardiovascular morbidity and mortality than office (casual) blood pressure measurements (OBP). (Also, see ► Chap. 41, “The Role of ABPM in Evaluation of Hypertensive Target-Organ Damage.”) It provides a much higher number of readings and therefore highly reproducible average 24-h, day- and nighttime blood pressure values. Furthermore, a profile of blood pressure behavior and variability is obtained during a patient’s daily routine. ABPM is the only appropriate method to evaluate nocturnal blood pressure decline (dipping) or nocturnal hypertension and to identify patients with white coat hypertension (elevated OBP, normal ABPM) or masked hypertension (normal OBP, elevated ABPM) in treated and untreated individuals (Parati et al. 2014; Flynn et al. 2014). The 24-h efficacy and timing of antihypertensive medication (chronopharmacology) can be assessed and adjusted on the basis of ABPM (Witte et al. 1993).

Self-monitoring of BP (home BP) has been suggested as an alternative to ABPM in adults (Pickering 2002) and in children (Stergiou et al. 2007). Home BP measurements correspond better with the ABPM profile than OBP alone, are more consistent over the whole blood pressure range (Wühl et al. 2004), and yield a high degree of diagnostic specificity in combination with OBP.

However, home BP cannot replace ABPM in children: The maximum diagnostic sensitivity, achieved by combined home and office BP, is only 81%. Thus, the diagnosis of hypertension will be missed in one out of five children diagnosed as hypertensive by ABPM (Wühl et al. 2004). Moreover, the range of agreement of home BP with ABPM is unacceptably wide, albeit narrower than that of OBP. Finally, nocturnal BP dysregulation or hypertension, being highly prevalent in children with chronic kidney disease, cannot be assessed by any daytime BP measurement.

Performing ABPM profiles for shorter periods of time has been suggested in order to reduce costs and measurement burden for the patient. However, a comparative study in children demonstrated that 6-h ABPM recordings correctly identified 94% of normotensive patients proven by 24-h ABPM results, but misclassified 54% of hypertensive patients as having a normal BP. Therefore, 6-h ABPM could be a cost-effective tool to evaluate white coat hypertension in children highly suspicious for having WCH but cannot replace 24-h ABPM (King-Schultz et al. 2012).

*White coat hypertension* is defined as OBP levels  $\geq$  95th percentile but normal out-of-office BP measurements (Home BP or ABPM). WCH may contribute to a misclassification of hypertension and unnecessary antihypertensive treatment. It may represent an intermediate pathophysiological stage between normotension and hypertension (Gustavsen et al. 2003) and may be associated with TOD, such as increased LVM (Kavey et al. 2007; Lande et al. 2008; Litwin et al. 2009; Pall et al. 2010), increased carotid intima media thickness (cIMT) (Litwin et al. 2009; Pall et al. 2010), and abnormalities in BP and heart rate rhythmicity (Litwin et al. 2010). WCH prevalence in children varies between 13% and 60% in the literature (Jurko et al. 2016). These differences can be partially explained by regional demographic and anthropometric variabilities. WCH is defined as temporary increase in blood pressure before and during visits in the clinic. It presumably represents a stress response associated with health care appointments, generally more pronounced when

BP is taken by a physician than by a nurse. Some authors define *white coat effect* as a difference of 5 or more mmHg between the average blood pressure in the clinic and home environment (Matsuoka et al. 2002).

*Masked hypertension* (MH) is defined as normal OBP but elevated ambulatory BP levels. The prevalence ranges from 7.6% to 15% in the literature (Lurbe et al. 2005; Stabouli et al. 2005; Furusawa et al. 2011) and MH may be more common in obese youths (19%), especially if they display a non-dipper pattern, i.e., evidence that the expected physiological decline in BP at night is blunted (Török et al. 2008). To diagnose MH is challenging – to determine the true prevalence of MH, use of ABPM in large unselected populations would be required. However, the diagnosis of MH is unlikely when the casual BP is found to be in the low normal range (Mitsnefes et al. 2016). A prior history of clinically important elevated BP, the presence of left ventricular hypertrophy, or other signs of TOD are suggestive of MH. Left ventricular mass (LVM) was found to be higher in patients with MH than in normotensive people and was similar to LVM in people with sustained hypertension. This observation implies a similar cardiovascular risk for MH as for sustained hypertension and suggests that MH may predict TOD (Lurbe et al. 2005; Stabouli et al. 2005; Verberk et al. 2008).

Masked hypertension can be safely diagnosed by ABPM in specific high-risk patient cohorts including pediatric dialysis patients who have been noted to have increasing BP levels between dialysis sessions (Chaudhuri et al. 2011) and in youths with type 1 diabetes mellitus (Sulakova et al. 2009).

*Nocturnal hypertension* has been cited as a predictor of clinical outcome in various patient populations, including chronic kidney disease (CKD), diabetes mellitus, and solid organ transplant patients (Lurbe et al. 2002; Ettinger et al. 2005; McGlothlan et al. 2006; Redon et al. 2010; Fan et al. 2010; Lee et al. 2011; Samuels et al. 2012). Isolated nocturnal hypertension can be only diagnosed by ABPM. Patients with isolated abnormalities of sleep BP should be considered as

having MH (Flynn et al. 2014). Most probably, nocturnal hypertension should be given the same interest as abnormalities of awake BP.

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### Limitations of Ambulatory Blood Pressure Monitoring

One major limitation of ABPM is the limited availability of a device in general practice settings and therefore, required referral of patients with suspected hypertension based on OBP to a hypertension specialist for confirmation of hypertension.

The ABPM measurement itself may cause discomfort, particularly at night. Some patients may be reluctant to have repeat measurements.

The nocturnal BP readings may disturb sleep and, thus, might have some impact on nocturnal BP level and dipping. ABPM findings and interpretation can also be influenced by possible inaccurate or invalid readings during activity or, less expected in resting periods. In addition, the ABPM analysis program may occasionally not be able to identify artificial measurement results. Another limitation results from the type of the available normative data. The present norms are from Caucasian children and normative data in other racial groups are lacking.

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### Cost Effectiveness of Ambulatory Blood Pressure Monitoring

Recommendation of a universal BP screening is still a matter of debate. Although the US Preventive Services Task Force Report questions the utility of universal BP screening at present, it is likely that rising obesity prevalence with rising frequency of BP screening will increase referrals to hypertension specialist. As OBP and Home BP are not able to reliably predict hypertension with ABPM, universal ABPM may be the most economically and clinically efficient diagnostic strategy for the initial diagnostic assessment of referred patients (Davis et al. 2014).

Currently, a number of authorities recommend ABPM as a cost-effective investigation, mainly based on its ability to identify white coat hypertension and to avert the need for antihypertensive

therapy in patients with a transient increase in BP. While ABPM is particularly cost-effective for the diagnosis and management of newly diagnosed hypertension, the reimbursement for the procedure varies considerably from country to country. Indeed, many countries do not provide any reimbursement (Parati et al. 2014). Furthermore, more research is needed to assess the best strategy for diagnosing masked hypertension. A reasonable approach may be to perform ABPM in patients with OBP values in the upper normal or prehypertensive range or presence of other cardiovascular risk factors (Wang et al. 2013).

Moreover, cost savings from avoiding treatment among white coat hypertensives or preventing future target organ damage in patients with MH are difficult to compute and will require a long follow-up time, possibly over decades.

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### Indications for Ambulatory Blood Pressure Monitoring

ABPM should be performed in all patients with elevated OBP to confirm the diagnosis of hypertension and to exclude WCH before starting antihypertensive treatment. Recent adult guidelines (Leung et al. 2016) recommend to restrict ABPM to patients with OBP values in the upper normal range or with mildly elevated BP (high-normal BP/prehypertension/hypertension stage I), as it is more likely for patients with low normal OBP or hypertension stage II to be true ABPM normotensives or hypertensives, respectively (Leung et al. 2016; Mitsnefes et al. 2016). However, this recommendation is questionable as ABPM provides far more information than mere median BP values. Thus, ABPM is recommended to confirm the diagnosis of hypertension in the most recent European and American childhood hypertension guidelines (Lurbe et al. 2016; Flynn et al. 2017).

ABPM is a helpful tool to evaluate blood pressure control in patients with confirmed hypertension on antihypertensive treatment and to exclude white coat hypertension (false resistant hypertension), hypotension, masked HTN, and uncontrolled nocturnal hypertension, especially in patients with secondary hypertension. Both

isolated daytime and nighttime hypertension can only be diagnosed by ABPM and are associated with an increased CV risk (O'Flynn et al. 2015).

Performing comprehensive ABPM evaluation is especially advisable in children and adolescents with CKD, diabetes mellitus type 1, obstructive sleep apnea, cardiac or endocrine hypertension, autonomic dysfunction, genetic risk for hypertension, and other high-risk patients (e.g., post-cardiac surgery patients, solid organ transplants, patients receiving drugs known to increase BP, patients at increased risk for TOD or with already existing TOD) (Flynn et al. 2014; Lurbe et al. 2016).

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## Methods for Ambulatory Blood Pressure Monitoring

### Ambulatory Blood Pressure Monitors

All recent guidelines include recommendations on the use of ABPM in diagnosing and treating high blood pressure in adults as well as in children (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004; 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension 2013; Armstrong and Joint National Committee 2014; Parati et al. 2014; Flynn et al. 2014; Lurbe et al. 2016). However, the equipment tested and approved for adults is often not explicitly validated in children. The ideal device should be validated for measurements in children, light-weight, equipped with small cuff sizes starting from the infant range, and should have a robust hardware and software suitable for use in physically active children without producing too many erroneous measurements (Urbina et al. 2008).

As for casual BP measurements, the cuff width should cover at least 40%, and the cuff length 80% to 100% of the upper arm circumference (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and

Adolescents 2004). Cuffs are available starting from neonate size; however, validation data for the youngest age group are missing. Standard cuff sizes for the use in infants start at 12 cm upper arm circumference. This cuff size will allow exact ABPM measurements from the age of 6 months onward. Measurements in infants younger than 2 years of age are technically feasible. The number of erroneous measurements seems to be even lower than in the 3–5 year olds (Gellermann et al. 1997; Varda and Gregoric 2005), possibly due to greater physical activity and lower acceptance of the measurement procedure in preschool age. However, normative data sets for infancy are still restricted to small sample sizes (Gellermann et al. 1997; Varda and Gregoric 2005).

Regarding measurement technology, both auscultatory and oscillometric ABPM devices are available. The limitations of both methods are comparable to those described for casual BP devices (Park et al. 2001; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004): Auscultatory ABPM devices are better graded regarding accuracy and durability according to national US (AAMI, (Association for the Advancement of Medical Instrumentation/American National Standards Institute 2002)) and British protocols (BHS (O'Brian et al. 1993)). Nevertheless, measurements are more prone to movement artifacts and the controversy which Korotkoff sound more accurately defines diastole (K4 vs. K5) has not been uniformly solved by the manufacturers. Moreover, comprehensive normative data for auscultatory ABPM devices are lacking. Oscillometric devices usually have less erroneous measurements than auscultatory devices (4% vs. 30% of measurements (O'Sullivan et al. 1999)) and are easier to use, although grading according to AAMI or BHS standard protocols is lower.

Systole and diastole are not measured directly but derived mathematically from mean arterial pressure by device specific algorithms; as a result differences between oscillometric measurements and auscultatory devices used for validation are common (Park et al. 2001). It should be also considered that published normative data might



be device specific. However, most published normative ABPM values are oscillometric data (Lurbe et al. 1994; Reichert et al. 1995; Gellermann et al. 1997; Soergel et al. 1997; Wühl et al. 2002; Varda and Gregoric 2005), and oscillometric devices are widely used in pediatric hypertension clinics.

Information on currently available ABPM monitors that have undergone independent testing and passed national standards (AAMI or BHS) is provided by the website [www.dableducational.org](http://www.dableducational.org) or the respective websites of the national hypertension leagues (e.g., American Society of Hypertension, British Hypertension Society, Deutsche Hochdruckliga). Only devices that have passed these tests and validated in the pediatric age group should be used in clinical practice.

### **Editing Ambulatory Blood Pressure Monitoring Data**

The software equipment of ABPM devices is variable. As a minimum requirement the frequency of measurements should be individually programmable and the software should enable entering pediatric 95th percentile cutoffs for ABPM norms (e.g., Soergel et al. 1997; Wühl et al. 2002, see Table 1). The mean 24-h, daytime and nighttime systolic, diastolic, and mean arterial pressure as well as BP load should be reported. Mean BP levels should be compared with normative values. In addition, the nocturnal BP dipping, i.e., the percent day-night difference ((mean daytime BP – mean nighttime BP)/mean daytime BP × 100), should be determined for systolic and diastolic BP. Variables used in ABPM studies are summarized in Table 2.

The recommended frequency for ABPM measurements is 15–20 min during daytime and 20–30 (to 60) min during nighttime, resulting in at least 40–50 readings within 24 h and at least one valid reading per nighttime hour. Gaps should not be longer than 2 h. A low frequency of measurements or shorter measurement duration is more comfortable for the patient but limits the validity of the individual profile. For analyses of blood pressure

rhythmicity (ultradian rhythms) intervals of 15–20 min during daytime and 20–30 min during nighttime are recommended (Hadtstein et al. 2004).

The ABPM recording should be edited for outliers by visual inspection of the profile. The ABPM software program should exclude BP readings out of the preset cutoff range a priori (e.g., systolic BP < 60 or > 220 mmHg, diastolic BP < 35 or > 120 mmHg, heart rate < 40 or > 180 bpm, pulse pressure < 40 or > 120 mmHg) (Urbina et al. 2008).

All patients should be instructed to fill in a diary on physical activity, rest and sleeping times, and drug intake. This is important to account for different levels of physical activity during BP recording and the effect of antihypertensive medication. Day- and nighttime (awake and sleeping periods) should be analyzed as reported in the patient's diary (Flynn 2002; Ettinger et al. 2005). If information is not available, the time period from 8 am to 8 pm might be chosen for daytime, and from midnight to 6 am for nighttime BP evaluation. This approach discards readings obtained during transition times (i.e., 6–8 am and 10 pm to midnight) from the analysis (Soergel et al. 1997). Preliminary data suggest that actual sleeping and waking times, determined by an actigraph, a wrist device sensing motion, may be superior to patient-initiated diary entry (Eissa et al. 2001).

Physical activity influences the success of BP measurements and BP itself. Simultaneous recording of activity by actigraphs shows that reliable and reproducible ABPM is feasible and that activity increases SBP and DBP by up to 10 mmHg (Portman et al. 1991). While undergoing ABPM children should continue normal activities except contact sports, vigorous exercise, and swimming. The child should be shown how the arm on which the BP cuff is placed should be held still during individual measurements to avoid erroneous readings.

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### **Applying the Device**

The personnel applying the ABP monitors should be fully trained on the maintenance, application, and function of the device and its components.

**Table 1** Ambulatory blood pressure values for healthy Caucasian children

(a) Normative ABPM values (mmHg) for boys by age (years)												
BP percentile	Age (years)											
	5.0	6.0	7.0	8.0	9.0	10.0	11.0	12.0	13.0	14.0	15.0	16.0
24-h SBP												
50th	104.6	105.5	106.3	107.0	107.7	108.8	110.4	112.6	115.1	117.8	120.6	123.4
75th	109.0	110.0	111.0	111.9	112.8	114.1	115.9	118.2	120.9	123.7	126.5	129.4
90th	113.4	114.7	115.8	116.8	117.9	119.2	121.2	123.7	126.4	129.3	132.1	134.9
95th	116.4	117.7	118.9	120.0	121.1	122.5	124.6	127.1	129.9	132.7	135.5	138.2
99th	122.7	124.1	125.4	126.6	127.7	129.2	131.4	134.0	136.9	139.5	142.0	144.5
Daytime SBP												
50th	111.1	111.5	111.9	112.2	112.6	113.4	114.9	117.0	119.5	122.3	125.3	128.2
75th	115.7	116.3	116.8	117.3	117.9	118.8	120.5	122.9	125.6	128.5	131.5	134.6
90th	120.1	120.9	121.6	122.2	122.9	124.0	125.9	128.4	131.2	134.2	137.3	140.4
95th	122.9	123.8	124.6	125.3	126.1	127.3	129.3	131.8	134.7	137.7	140.8	143.9
99th	128.5	129.6	130.6	131.5	132.3	133.7	135.8	138.6	141.5	144.4	147.4	150.4
Nighttime SBP												
50th	95.0	95.5	96.1	96.7	97.3	98.1	99.4	101.2	103.4	105.8	108.3	110.9
75th	99.2	100.2	101.1	102.0	102.9	103.9	105.3	107.1	109.3	111.9	114.4	116.9
90th	103.4	104.9	106.2	107.5	108.5	109.6	111.0	112.8	115.0	117.5	120.0	122.5
95th	106.3	108.0	109.6	111.0	112.1	113.2	114.6	116.3	118.6	121.0	123.4	125.9
99th	112.3	114.6	116.7	118.4	119.6	120.7	121.9	123.4	125.5	127.8	130.1	132.3
24-h DBP												
50th	65.3	65.7	66.1	66.3	66.5	66.6	66.9	67.2	67.4	67.7	68.1	68.6
75th	68.8	69.3	69.6	69.9	70.0	70.2	70.5	70.8	71.0	71.4	71.8	72.3
90th	72.2	72.6	73.0	73.2	73.3	73.4	73.7	74.0	74.3	74.6	75.1	75.6
95th	74.4	74.8	75.1	75.2	75.3	75.4	75.7	75.9	76.2	76.6	77.0	77.5
99th	78.9	79.0	79.1	79.1	79.1	79.1	79.3	79.6	79.9	80.2	80.7	81.3
Daytime DBP												
50th	72.2	72.4	72.5	72.5	72.3	72.1	72.0	72.0	72.2	72.5	73.0	73.5
75th	75.9	76.1	76.3	76.4	76.2	76.0	76.0	76.0	76.2	76.5	77.0	77.6
90th	79.1	79.3	79.7	79.8	79.7	79.5	79.5	79.5	79.7	80.0	80.6	81.3
95th	81.0	81.3	81.6	81.8	81.7	81.5	81.5	81.6	81.7	82.1	82.8	83.5
99th	84.5	84.8	85.2	85.5	85.4	85.3	85.3	85.4	85.6	86.1	86.8	87.7
Nighttime DBP												
50th	55.0	55.3	55.5	55.7	55.8	55.8	55.9	56.0	56.3	56.5	56.8	57.1
75th	58.5	59.1	59.5	59.8	60.0	60.0	60.0	60.1	60.3	60.5	60.7	60.9
90th	62.3	63.2	63.8	64.2	64.3	64.2	64.1	64.1	64.1	64.2	64.3	64.3
95th	65.1	66.1	66.8	67.1	67.1	66.9	66.7	66.5	66.5	66.5	66.4	66.4
99th	71.6	72.7	73.5	73.5	73.2	72.6	71.9	71.4	71.1	70.8	70.6	70.3
24-h MAP												
50th	77.4	77.9	78.7	79.3	79.7	80.2	80.8	81.7	82.7	83.8	85.1	86.4
75th	81.4	81.9	82.7	83.4	83.8	84.3	85.0	85.9	86.9	88.0	89.3	90.5
90th	85.5	86.0	86.8	87.4	87.9	88.3	88.9	89.7	90.6	91.6	92.7	93.9
95th	88.3	88.7	89.5	90.0	90.4	90.8	91.3	91.9	92.7	93.7	94.7	95.7
99th	94.3	94.6	95.1	95.4	95.6	95.7	95.8	96.2	96.7	97.3	98.1	98.9
Daytime MAP												
50th	83.5	84.1	84.5	84.8	84.9	85.0	85.3	85.9	86.8	88.0	89.4	90.8
75th	87.5	88.2	88.8	89.2	89.4	89.5	89.9	90.6	91.5	92.7	94.2	95.7
90th	91.3	92.1	92.8	93.3	93.5	93.7	94.0	94.7	95.6	96.8	98.3	99.8

(continued)

**Table 1** (continued)

(a) Normative ABPM values (mmHg) for boys by age (years)

BP percentile	Age (years)											
	5.0	6.0	7.0	8.0	9.0	10.0	11.0	12.0	13.0	14.0	15.0	16.0
95th	93.6	94.5	95.3	95.8	96.1	96.2	96.5	97.1	98.0	99.2	100.6	102.1
99th	98.2	99.2	100.1	100.7	101.0	101.0	101.2	101.6	102.4	103.4	104.7	106.1

Nighttime MAP

50th	66.7	67.7	68.6	69.2	69.7	70.0	70.5	71.2	72.1	73.1	74.0	74.9
75th	70.5	71.7	72.8	73.5	74.1	74.5	75.0	75.6	76.4	77.2	78.0	78.6
90th	74.7	76.0	77.2	78.1	78.6	78.9	79.3	79.7	80.3	80.8	81.3	81.7
95th	77.6	79.0	80.2	81.1	81.6	81.8	82.0	82.3	82.6	82.9	83.2	83.4
99th	84.1	85.7	86.9	87.6	87.8	87.7	87.4	87.1	86.9	86.8	86.6	86.4

(b) Normative ABPM values (mmHg) for boys by height (in centimeters)

BP percentile	Height (cm)													
	120.0	125.0	130.0	135.0	140.0	145.0	150.0	155.0	160.0	165.0	170.0	175.0	180.0	185.0

24-h SBP

50th	104.5	105.3	106.2	107.2	108.3	109.5	110.9	112.5	114.2	116.1	118.0	119.7	121.5	123.2
75th	109.2	110.1	111.1	112.1	113.3	114.6	116.1	117.7	119.5	121.4	123.2	125.0	126.6	128.2
90th	113.8	114.8	115.9	116.9	118.2	119.5	121.0	122.6	124.4	126.3	128.1	129.8	131.3	132.8
95th	116.8	117.8	118.9	120.0	121.2	122.5	124.0	125.7	127.4	129.3	131.1	132.6	134.1	135.5
99th	122.9	123.9	125.0	126.1	127.3	128.6	130.1	131.7	133.4	135.2	136.8	138.2	139.4	140.5

Daytime SBP

50th	110.8	111.1	111.5	112.0	112.7	113.7	115.1	116.8	118.6	120.6	122.6	124.4	126.2	128.0
75th	116.2	116.5	116.9	117.4	118.0	119.0	120.4	122.1	124.2	126.4	128.4	130.3	132.2	134.1
90th	121.7	121.9	122.2	122.5	123.0	123.9	125.3	127.1	129.4	131.9	134.1	136.1	138.0	139.9
95th	125.2	125.3	125.5	125.7	126.0	126.9	128.3	130.2	132.7	135.3	137.6	139.6	141.6	143.5
99th	132.6	132.4	132.2	132.0	132.1	132.8	134.2	136.3	139.1	142.2	144.7	146.8	148.6	150.5

Nighttime SBP

50th	93.6	94.6	95.6	96.7	97.9	99.0	100.1	101.3	102.6	104.1	105.6	107.2	108.7	110.2
75th	98.6	99.8	101.0	102.3	103.6	104.7	105.9	107.1	108.4	109.9	111.5	113.1	114.6	116.1
90th	103.3	104.8	106.3	107.8	109.3	110.6	111.8	113.0	114.3	115.7	117.2	118.8	120.3	121.8
95th	106.3	107.9	109.7	111.4	113.0	114.4	115.7	116.8	118.1	119.4	120.9	122.4	123.9	125.3
99th	112.1	114.2	116.5	118.7	120.8	122.5	123.8	124.9	126.0	127.1	128.4	129.6	131.0	132.2

24-h DBP

50th	65.6	65.9	66.1	66.4	66.6	66.9	67.1	67.2	67.3	67.5	67.6	67.8	68.0	68.2
75th	69.7	69.9	70.2	70.4	70.6	70.8	71.0	71.1	71.2	71.3	71.5	71.7	71.8	71.9
90th	73.9	74.1	74.2	74.4	74.5	74.7	74.8	74.8	74.9	75.1	75.3	75.4	75.5	75.6
95th	76.7	76.8	76.9	76.9	77.0	77.1	77.1	77.2	77.3	77.5	77.7	77.8	77.9	78.0
99th	82.7	82.5	82.3	82.1	81.9	81.8	81.8	81.8	81.9	82.2	82.5	82.7	82.9	83.0

Daytime DBP

50th	72.3	72.3	72.2	72.1	72.1	72.1	72.1	72.1	72.2	72.3	72.6	72.8	73.1	73.4
75th	76.5	76.4	76.3	76.2	76.0	76.0	75.9	75.9	76.0	76.2	76.5	76.8	77.2	77.5
90th	80.2	80.1	79.9	79.7	79.5	79.4	79.3	79.3	79.4	79.7	80.0	80.5	80.9	81.3
95th	82.4	82.2	82.0	81.8	81.5	81.4	81.2	81.2	81.3	81.7	82.1	82.6	83.1	83.6
99th	86.5	86.2	85.9	85.6	85.2	85.0	84.8	84.8	85.0	85.4	86.0	86.6	87.3	87.9

Nighttime DBP

50th	54.3	54.8	55.1	55.5	55.8	56.0	56.2	56.2	56.3	56.5	56.7	56.9	57.1	57.3
75th	57.6	58.2	58.8	59.2	59.6	59.9	60.1	60.2	60.2	60.3	60.5	60.6	60.8	60.9
90th	60.7	61.4	62.1	62.7	63.2	63.5	63.7	63.8	63.8	63.9	63.9	64.0	64.1	64.2
95th	62.6	63.4	64.2	64.8	65.4	65.8	66.0	66.0	66.0	66.0	66.1	66.1	66.1	66.2

(continued)

**Table 1** (continued)

(b) Normative ABPM values (mmHg) for boys by height (in centimeters)														
BP percentile	Height (cm)													
	120.0	125.0	130.0	135.0	140.0	145.0	150.0	155.0	160.0	165.0	170.0	175.0	180.0	185.0
99th	66.2	67.2	68.2	69.0	69.7	70.1	70.4	70.4	70.3	70.3	70.2	70.1	70.0	69.9
24-h MAP														
50th	77.5	78.1	78.7	79.3	79.9	80.5	81.1	81.7	82.3	83.1	83.9	84.7	85.5	86.3
75th	81.8	82.4	83.0	83.5	84.1	84.6	85.2	85.9	86.6	87.3	88.1	89.0	89.8	90.7
90th	86.3	86.7	87.2	87.6	88.0	88.5	89.1	89.7	90.3	91.1	91.9	92.7	93.5	94.3
95th	89.3	89.6	89.9	90.2	90.5	90.9	91.4	91.9	92.6	93.3	94.0	94.8	95.6	96.4
99th	95.9	95.7	95.5	95.4	95.4	95.6	95.9	96.3	96.7	97.4	98.0	98.7	99.4	100.1
Daytime MAP														
50th	83.8	84.1	84.3	84.5	84.7	85.0	85.4	85.8	86.4	87.1	88.0	89.0	90.0	91.0
75th	88.5	88.7	88.9	89.0	89.1	89.4	89.6	90.1	90.7	91.6	92.6	93.7	94.9	96.1
90th	92.9	93.0	93.1	93.1	93.1	93.2	93.4	93.8	94.5	95.4	96.5	97.7	99.0	100.3
95th	95.6	95.6	95.6	95.5	95.5	95.5	95.7	96.0	96.7	97.7	98.8	100.1	101.4	102.8
99th	101.0	100.7	100.5	100.2	99.9	99.7	99.8	100.1	100.8	101.7	102.9	104.3	105.7	107.1
Nighttime MAP														
50th	66.8	67.6	68.3	69.0	69.6	70.1	70.6	71.2	71.9	72.7	73.6	74.5	75.4	76.2
75th	71.0	71.9	72.7	73.4	73.9	74.4	74.9	75.4	76.0	76.8	77.6	78.3	79.1	79.8
90th	75.9	76.6	77.3	77.9	78.3	78.6	78.9	79.2	79.7	80.3	80.9	81.5	82.1	82.7
95th	79.5	80.0	80.5	80.9	81.2	81.3	81.4	81.5	81.9	82.3	82.8	83.3	83.8	84.3
99th	88.4	88.1	87.8	87.6	87.2	86.7	86.3	86.0	86.0	86.1	86.3	86.5	86.8	87.0
(c) Normative ABPM values (mmHg) for girls by age (years)														
BP percentile	Age (years)													
	5.0	6.0	7.0	8.0	9.0	10.0	11.0	12.0	13.0	14.0	15.0	16.0		
24-h SBP														
50th	102.8	104.1	105.3	106.5	107.6	108.7	109.7	110.7	111.8	112.8	113.8	114.8		
75th	107.8	109.1	110.4	111.5	112.6	113.6	114.7	115.7	116.7	117.6	118.4	119.2		
90th	112.3	113.7	115.0	116.1	117.2	118.2	119.2	120.2	121.2	121.9	122.6	123.2		
95th	114.9	116.4	117.7	118.9	120.0	121.1	122.1	123.0	123.9	124.5	125.0	125.6		
99th	119.9	121.5	123.0	124.3	125.5	126.5	127.5	128.4	129.0	129.5	129.7	130.0		
Daytime SBP														
50th	108.4	109.5	110.6	111.5	112.4	113.3	114.2	115.3	116.4	117.5	118.6	119.6		
75th	113.8	114.9	115.9	116.8	117.6	118.5	119.5	120.6	121.7	122.6	123.5	124.3		
90th	118.3	119.5	120.6	121.5	122.4	123.3	124.3	125.3	126.4	127.2	127.9	128.5		
95th	120.9	122.2	123.3	124.3	125.2	126.2	127.2	128.2	129.2	129.9	130.4	130.9		
99th	125.6	127.1	128.4	129.6	130.6	131.7	132.7	133.7	134.5	135.0	135.2	135.4		
Nighttime SBP														
50th	94.8	95.6	96.2	96.8	97.5	98.2	99.0	99.7	100.5	101.3	102.0	102.9		
75th	100.2	101.1	101.8	102.5	103.2	104.0	104.7	105.2	105.8	106.3	106.8	107.3		
90th	105.3	106.3	107.2	108.0	108.8	109.5	110.1	110.4	110.7	110.9	111.0	111.2		
95th	108.4	109.6	110.6	111.5	112.3	113.0	113.5	113.6	113.7	113.6	113.5	113.5		
99th	114.5	116.0	117.3	118.4	119.3	119.9	120.1	119.8	119.4	118.8	118.2	117.8		
24-h DBP														
50th	65.5	65.6	65.8	65.9	66.0	66.2	66.4	66.6	67.0	67.2	67.5	67.7		
75th	68.9	69.1	69.2	69.3	69.5	69.8	70.0	70.4	70.8	71.1	71.2	71.4		
90th	72.1	72.2	72.3	72.4	72.6	72.9	73.2	73.7	74.1	74.4	74.6	74.7		
95th	74.0	74.1	74.2	74.2	74.4	74.7	75.1	75.6	76.1	76.4	76.6	76.7		
99th	77.6	77.6	77.6	77.6	77.7	78.0	78.4	79.1	79.7	80.1	80.4	80.5		

(continued)

**Table 1** (continued)

(c) Normative ABPM values (mmHg) for girls by age (years)

BP percentile	Age (years)											
	5.0	6.0	7.0	8.0	9.0	10.0	11.0	12.0	13.0	14.0	15.0	16.0
Daytime DBP												
50th	72.6	72.6	72.4	72.2	72.0	71.8	71.8	72.1	72.4	72.8	73.2	73.5
75th	76.7	76.6	76.5	76.3	76.0	75.9	75.9	76.2	76.5	76.8	77.0	77.2
90th	80.2	80.2	80.0	79.8	79.5	79.3	79.4	79.6	80.0	80.2	80.3	80.3
95th	82.3	82.2	82.1	81.8	81.5	81.3	81.4	81.6	82.0	82.2	82.2	82.1
99th	86.1	86.0	85.8	85.5	85.2	85.0	85.0	85.3	85.6	85.7	85.6	85.4
Nighttime DBP												
50th	56.4	55.9	55.5	55.1	54.8	54.6	54.3	54.2	54.3	54.5	54.9	55.3
75th	61.1	60.6	60.1	59.7	59.4	59.2	58.9	58.7	58.7	58.7	58.8	59.1
90th	65.6	65.1	64.6	64.1	63.8	63.7	63.4	63.1	62.9	62.8	62.8	62.8
95th	68.5	67.9	67.4	66.9	66.6	66.5	66.2	65.9	65.6	65.4	65.3	65.2
99th	74.2	73.6	72.9	72.4	72.2	72.0	71.8	71.4	71.1	70.7	70.3	70.0
24-h MAP												
50th	77.5	78.0	78.4	78.8	79.2	79.6	80.2	80.9	81.5	82.2	82.7	83.0
75th	81.2	81.7	82.1	82.5	82.9	83.3	84.0	84.7	85.4	86.0	86.5	86.8
90th	84.6	85.0	85.4	85.7	86.1	86.5	87.1	87.9	88.6	89.2	89.7	89.9
95th	86.6	87.0	87.3	87.6	87.9	88.3	88.9	89.7	90.5	91.0	91.5	91.7
99th	90.5	90.8	90.9	91.0	91.2	91.6	92.2	93.0	93.7	94.2	94.6	94.8
Daytime MAP												
50th	83.7	83.9	84.0	84.1	84.2	84.4	84.7	85.2	85.9	86.5	87.1	87.7
75th	88.2	88.3	88.4	88.4	88.4	88.5	88.9	89.4	90.1	90.8	91.4	91.9
90th	92.2	92.2	92.2	92.1	92.0	92.1	92.4	93.0	93.6	94.3	94.8	95.4
95th	94.6	94.5	94.4	94.2	94.1	94.2	94.4	95.0	95.6	96.2	96.8	97.3
99th	99.0	98.7	98.5	98.2	97.9	97.9	98.1	98.6	99.2	99.7	100.2	100.7
Nighttime MAP												
50th	68.7	68.8	68.8	68.8	68.9	69.1	69.3	69.6	70.1	70.6	71.2	71.8
75th	73.0	73.1	73.1	73.2	73.4	73.6	73.8	74.1	74.5	74.9	75.4	75.9
90th	76.9	77.0	77.1	77.2	77.4	77.6	77.8	78.0	78.3	78.6	78.9	79.3
95th	79.2	79.4	79.6	79.7	79.8	80.1	80.2	80.3	80.5	80.7	80.9	81.2
99th	83.8	84.1	84.2	84.3	84.5	84.6	84.7	84.6	84.6	84.6	84.6	84.7

(d) Normative ABPM values (mmHg) for girls by height (in centimeters)

BP percentile	Height (cm)											
	120.0	125.0	130.0	135.0	140.0	145.0	150.0	155.0	160.0	165.0	170.0	175.0
24-h SBP												
50th	104.0	105.0	106.0	106.8	107.6	108.7	109.9	111.2	112.4	113.7	115.0	116.4
75th	108.2	109.3	110.3	111.2	112.1	113.2	114.6	115.9	117.0	118.0	119.2	120.4
90th	112.0	113.2	114.3	115.3	116.2	117.4	118.7	120.0	121.0	121.8	122.8	123.8
95th	114.3	115.6	116.7	117.7	118.7	119.9	121.2	122.5	123.3	124.1	124.9	125.8
99th	118.8	120.1	121.3	122.4	123.4	124.6	126.0	127.1	127.7	128.2	128.8	129.3
Daytime SBP												
50th	110.0	110.5	111.0	111.6	112.2	113.1	114.3	115.6	117.0	118.3	119.8	121.2
75th	114.4	115.0	115.7	116.3	117.0	118.1	119.4	120.7	121.9	123.1	124.2	125.3
90th	118.2	119.0	119.7	120.4	121.3	122.5	123.9	125.2	126.4	127.3	128.1	128.9
95th	120.4	121.3	122.1	122.9	123.8	125.1	126.5	127.9	129.1	129.8	130.5	131.0
99th	124.5	125.5	126.4	127.4	128.5	129.9	131.5	133.0	134.0	134.5	134.8	135.0

(continued)

**Table 1** (continued)

(d) Normative ABPM values (mmHg) for girls by height (in centimeters)

BP percentile	Height (cm)											
	120.0	125.0	130.0	135.0	140.0	145.0	150.0	155.0	160.0	165.0	170.0	175.0
Nighttime SBP												
50th	95.0	95.7	96.4	96.9	97.5	98.1	98.9	100.0	101.1	102.2	103.4	104.6
75th	99.4	100.3	101.2	101.9	102.6	103.4	104.4	105.5	106.4	107.3	108.2	109.2
90th	103.3	104.4	105.5	106.5	107.5	108.5	109.5	110.5	111.2	111.8	112.4	113.1
95th	105.6	106.9	108.1	109.3	110.4	111.6	112.7	113.6	114.1	114.4	114.8	115.3
99th	109.8	111.5	113.1	114.7	116.2	117.7	118.9	119.5	119.6	119.4	119.3	119.4
24-h DBP												
50th	65.9	65.9	66.0	66.1	66.2	66.3	66.5	66.7	67.0	67.4	68.0	68.6
75th	68.6	68.9	69.2	69.5	69.8	70.1	70.4	70.6	70.7	71.0	71.3	71.6
90th	70.9	71.4	71.9	72.4	72.9	73.4	73.8	74.0	74.1	74.2	74.4	74.5
95th	72.2	72.8	73.4	74.1	74.7	75.3	75.7	76.0	76.1	76.2	76.2	76.2
99th	74.6	75.3	76.2	77.1	77.9	78.7	79.3	79.7	79.9	79.9	79.9	79.7
Daytime DBP												
50th	73.2	72.8	72.4	72.1	71.8	71.7	71.8	72.0	72.4	73.1	73.9	74.8
75th	76.9	76.6	76.4	76.2	76.1	76.1	76.1	76.2	76.4	76.8	77.3	77.8
90th	80.1	79.9	79.8	79.8	79.7	79.8	79.9	79.9	79.9	80.0	80.2	80.5
95th	81.9	81.8	81.8	81.8	81.9	82.0	82.0	82.0	82.0	81.9	82.0	82.0
99th	85.3	85.3	85.4	85.6	85.8	85.9	86.0	85.9	85.7	85.4	85.2	84.9
Nighttime DBP												
50th	55.4	55.3	55.1	54.8	54.6	54.4	54.3	54.4	54.6	54.9	55.1	55.4
75th	59.5	59.5	59.4	59.3	59.1	58.9	58.8	58.7	58.8	58.9	61.0	59.3
90th	63.1	63.3	63.4	63.4	63.3	63.1	63.0	62.9	62.9	62.9	66.9	63.1
95th	65.2	65.5	65.7	65.8	65.8	65.7	65.6	65.5	65.5	65.5	70.8	65.5
99th	69.1	69.6	70.1	70.4	70.6	70.8	70.8	70.7	70.7	70.6	79.0	70.4
24-h MAP												
50th	77.2	77.8	78.3	78.7	79.2	79.7	80.2	80.8	81.5	82.3	83.1	84.0
75th	80.6	81.2	81.8	82.4	82.9	83.5	84.1	84.7	85.3	85.9	86.6	87.4
90th	83.6	84.2	84.9	85.5	86.1	86.7	87.3	87.9	88.4	88.9	89.5	90.1
95th	85.3	86.0	86.7	87.4	88.0	88.6	89.2	89.7	90.2	90.6	91.1	91.7
99th	88.5	89.2	89.9	90.6	91.3	91.9	92.5	93.0	93.3	93.6	94.0	94.5
Daytime MAP												
50th	83.3	83.7	84.0	84.1	84.3	84.5	84.9	85.5	86.2	87.0	88.0	88.9
75th	87.4	87.9	88.2	88.5	88.7	88.9	89.3	89.8	90.3	90.9	91.6	92.2
90th	90.9	91.5	91.9	92.2	92.4	92.7	93.0	93.4	93.7	94.1	94.5	94.9
95th	92.9	93.6	94.0	94.4	94.6	94.9	95.1	95.4	95.6	95.8	96.1	96.4
99th	96.6	97.4	97.9	98.3	98.6	98.8	99.0	99.0	99.0	99.0	99.0	99.1
Nighttime MAP												
50th	68.0	68.2	68.4	68.5	68.7	69.0	69.3	69.8	70.4	71.2	72.0	72.8
75th	72.6	72.7	72.9	73.0	73.2	73.5	73.9	74.3	74.8	75.4	76.1	76.9
90th	76.8	76.9	77.0	77.2	77.4	77.7	78.0	78.3	78.6	79.1	79.6	80.3
95th	79.5	79.4	79.6	79.7	79.9	80.2	80.4	80.6	80.8	81.2	81.6	82.2
99th	84.6	84.4	84.5	84.6	84.8	85.0	85.0	85.0	85.0	85.0	85.3	85.6

Adapted from Wühl (2002), Urbina et al. (2008), and Sorof et al. (2014). Reprinted with permission Hypertension. 2014;63:1116–1135. Copyright American Heart Association, Inc.

**Table 2** ABPM parameters in clinical routine and research

ABPM parameter	Unit	Normal range	Definition
Clinical routine			
Mean SBP, DBP, MAP	mmHg	See Table 1	Calculation of mean values for daytime, nighttime, and 24 h periods for SBP, DBP, MAP
Nocturnal dipping	%	>10; Non-dipping: < 10% (reduced dipping 1–10%); Extreme dipping: > 20%; Reverse dipping: nocturnal BP increase	Percent day/night difference ((mean awake BP-mean sleep BP)/mean awake BP × 100) for both SBP and DBP
Load	%	<25	Percentage of readings above the ambulatory 95th percentile for both SBP and DBP during the entire 24-h, awake, and sleep periods
Research			
SBP, DBP, MAP percentiles, or z-scores		<95th percentile	Calculation of percentiles or z-scores (SDS) using normative, sex- and height (or age)-specific data obtained in large pediatric populations using similar techniques. Evaluation for daytime, nighttime, and 24 h periods (see corresponding section and Table 1)
Hyperbaric Index (HBI)	mmHg × h		Area under the curve for SBP and DBP readings above the 95th percentile
BP variability	mmHg		Standard deviation of mean SBP or DBP for a given time period
Morning surge	mmHg		Excessive systolic and/or diastolic BP elevation in the morning
Rate-pressure product			Rate pressure product ( $RPP$ ) = Heart rate ( $HR$ ) * systolic blood pressure ( $SBP$ )
Smoothness index (SI)			Average change (before and during treatment) in average hourly blood pressure values ( $[\Delta]H$ )/normalized SD of average change $SI = \frac{\Delta H}{SD_{\Delta H}}$
Ambulatory arterial stiffness index (AASI)			1 – (regression slope of DBP/SBP)
Midline estimating statistic of rhythm (MESOR) (Fourier analysis)	mmHg		Value midway between the highest and lowest values of the fitted cosine curve
Amplitude (Fourier analysis)	mmHg	See normative data (Hadtstein et al. 2004)	The distance between MESOR and the highest value of the cosine curve (= magnitude of rhythmic change)
Acrophase (Fourier analysis)	h	See normative data (Hadtstein et al. 2004)	Time of the highest value of the cosine curve, expressed as hours after midnight (= timing of rhythmic change)

The device needs to be maintained and calibrated in the manufacturer prescribed time intervals. The cuffs should be laundered regularly; some manufacturers sell single-use covers for the BP cuffs.

The device itself should be regularly cleaned with a wiping disinfectant.

A standardized protocol is recommended. Parents and patients should be informed how to

operate the monitor (e.g., stop a reading, turn off or restart the device). Although removal of the monitor is not recommended, if absolutely necessary, the device should be removed immediately after a reading (to reduce the number of missed readings) and reapplied as soon as possible. Contact of the electronic device with water must be avoided.

Serious adverse events have not been reported in children; however, mild disturbance of sleep, petechiae, or bruises have been observed (Prisant et al. 1996). Contraindications to ABPM may include atrial fibrillation, coagulation disorders, and, for some brands of equipment that contain latex, the presence of a latex allergy.

The accuracy and precision of the devices should be checked by simultaneous measurements with a sphygmomanometer at the beginning of each test period. The average difference between the mean of three clinic and three ABPM measurements should be less than 5 mmHg to consider adequate calibration. The cuff should be applied to the nondominant arm, in hemodialysis patients to the non-fistula arm. If SBP difference between arms is  $>10$  mmHg, the arm with the highest value obtained should be used.

Criteria for a successful ambulatory BP monitoring study are at least 70% of successful readings and at least 20 successful daytime and 7 nighttime readings (Soergel et al. 1997; Flynn et al. 2014; Parati et al. 2014; Leung et al. 2016).

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## Normative Ambulatory Blood Pressure Monitoring Data

While fixed, risk-adapted cutoff levels for optimal, normal, high-normal, and elevated office blood pressure have been defined for the adult population (2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension 2013; James et al. 2014), pediatric targets for OBP and ABPM are still derived from the distribution of BP in the general pediatric population.

Comparison with appropriate normative data stratified by gender and age or height is essential

for a meaningful interpretation of ABPM findings in the pediatric setting (see pediatric ABPM norms in Caucasian children in Table 1).

In childhood, BP is strongly influenced by body dimensions (Brotons et al. 1989; de Man et al. 1991; Lurbe et al. 1994; Reusz et al. 1994; Harshfield et al. 1994; Reichert et al. 1995; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004; Soergel et al. 1997). In addition, changes in body composition during puberty have profound gender-specific effects on BP. Furthermore, the level, timing, and duration of physical activity are markedly age and gender dependent. For example, median 24-h systolic BP increases across childhood by almost 19 mmHg in boys and 12 mmHg in girls, respectively (Wühl et al. 2002). Median values are virtually identical in boys and girls up to 11 years of age or 140 cm of height. During puberty, systolic BP increases more steeply in boys, resulting in a median difference of 8.4 mmHg at age 16 years. These differences are equally marked during day- and nighttime (Wühl et al. 2002).

In contrast to the marked increase in systolic BP, diastolic BP increases only minimally with age during childhood. The median increase in median 24-h diastolic BP over time was 3.3 and 2.2 mmHg in boys and girls, respectively (Wühl et al. 2002). This finding is in contrast to reference data for casual BP measurements (de Man et al. 1991; Update on the 1987 task force report on high blood pressure in children and adolescents: a working group report from the national high blood pressure educational program. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents 1996; Menghetti et al. 1999) and to at least one other ambulatory BP study where DBP varied with age (Harshfield et al. 1994). In addition, the age-related increase in systolic BP is less marked than in casual BP reference studies. These discrepancies might be explained by an increasing prevalence of the white coat phenomenon across childhood. However, technical artifacts, such as age-dependent differences in cuff size relative to upper arm circumference between manual and ABPM devices, cannot be completely ruled out. It is also possible that age-related differences in diastolic BP might be



related to difficulties in defining diastolic BP by Korotkoff phases IV and V by auscultatory BP measurements or to the use of invalidated algorithms implemented in oscillometric ABPM devices. However, even using auscultatory measurements, no systematic increase of mean diastolic BP with age was observed in an ABPM study assessing a large number of children aged 6–16 years, whereas systolic BP was clearly age dependent (O’Sullivan et al. 1999). Furthermore, the inclusion of only European white children limits the generalizability of the normative data (Soergel et al. 1997; Wühl et al. 2002), as there is evidence that normal ABPM limits may vary with ethnicity (Vaughan and Murphy 1994). Also, the number of children <140 cm in height was small, thus the applicability of the data to younger children with short stature, especially in chronic kidney disease, may be also limited (Flynn 2011).

However, despite these limitations, the reference values provided by the German Working Group on Pediatric Hypertension (Soergel et al. 1997; Wühl et al. 2002) are still considered the best available data for pediatric ABPM and are recommended by the American (Flynn et al. 2017) and European (Parati et al. 2014; Lurbe et al. 2016) hypertension guidelines.

Differences in the analysis of the data of the German Working Group on Pediatric Hypertension by Soergel and Wühl (Soergel et al. 1997; Wühl et al. 2002) resulted in small changes in the limit values that define ambulatory HTN, particularly for boys at the extremes of height. Therefore, for research purposes, either limit source is sufficient but must remain consistent over long-term projects (Bell et al. 2011).

In addition, that study established percentiles normalized for the non-Gaussian distribution of 24-h BP in Caucasian children according to age and sex, using the LMS analysis method (Wühl et al. 2002). The normative BP data are given in Table 1, the LMS data in Tables 5 and 6.

An overview on published pediatric ABPM normative data sets is given in Table 3, and, as noted, these are from studies in Caucasian children. Up to date, few large cross-sectional ABPM studies have been performed in healthy controls. The cutoff values for the normal range were

defined by the 95th percentile of the BP distribution in healthy children in all these studies. It should be recognized that ABPM BP values measured with an oscillometric device (Soergel et al. 1997; Wühl et al. 2002) tend to be higher than resting BP values obtained by auscultation (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). This difference will lead to a difference in the prevalence of hypertension or in misclassification of BP category when choosing the lower OBP references for the evaluation of ABPM. In a study by Sorof, white coat hypertension was diagnosed in only 31% of patients using the ambulatory criteria, whereas applying the lower casual BP cutoffs would result in 59% being diagnosed with white coat hypertension (Sorof et al. 2001).

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## Ambulatory Blood Pressure Monitoring Report and Interpretation

The ABPM analysis and report should be standardized independent of the device used. It should contain a standardized plot of all BP measurements (SBP, DBP, MAP, and heart rate) showing daytime (awake) and nighttime (sleep) periods and 95th percentiles for SBP and DBP over the 24-h period (for example see Fig. 1).

Ideally, the appropriate limits should be programmed into the ABPM software to minimize the need for subjective editing of ABPM data.

Average SBP, DBP, MAP, and heart rate for daytime, nighttime, and 24 h should be displayed as well as percent of nocturnal BP decline (dipping) for SBP and DBP, the percentage of measurements above the 95th BP percentile (load), or the area under the curve for BP readings above the 95th percentile (hyperbaric index).

The summary statistics should also include the information for time-weighted average systolic and diastolic BP, MAP, and heart rate for the 24-h period, daytime (awake), and nighttime (asleep), with standard deviations, trough, and peak BP values for each parameter and number of valid BP readings.

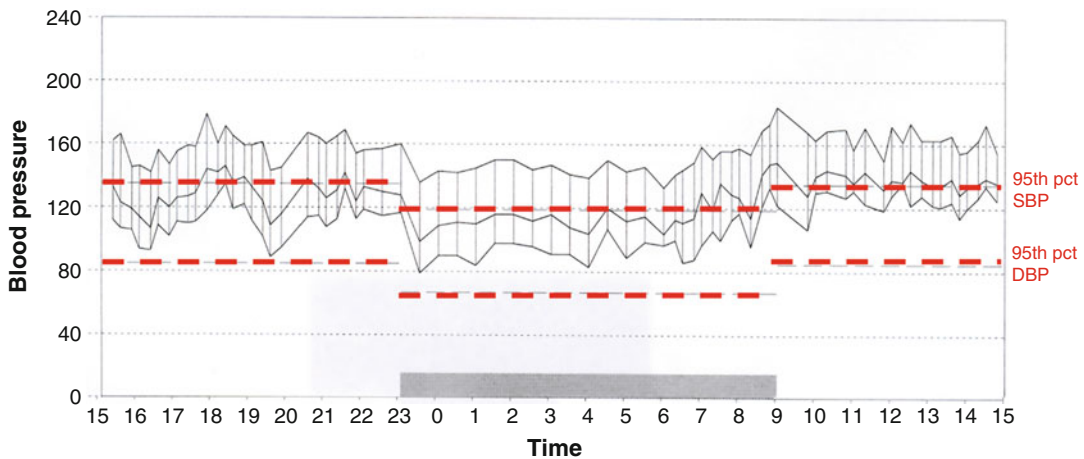
**Table 3** Published normative ABPM data sets

Author	No of subjects	Age range studied (years)	Method	Successful exams (%)	Successful readings (%)
Harshfield et al. (1994)	300	10–18	ausc + osc	84	85–90
Lurbe et al. (1994, 1999)	333	3–18	osc	84	89.8
O’Sullivan et al. (1999)	1121	6–16	ausc + osc	99.7	>95
Reichert et al. (1995)	564	9–13	ausc + osc	95	64
Soergel et al. (1997)	1254	5–21	osc	98.9	92.7
Wühl et al. (2002)	949 <sup>a</sup>	5–20	osc	<sup>a</sup>	<sup>a</sup>
Gellermann et al. (1997)	61	3–6	osc	77	46–58
Varda and Gregoric (2005)	97	0.1–2.5	osc	87	75

<sup>a</sup>Analysis of the data set from Soergel et al. (1997) by the LMS method (Cole and Green 1992)

Only complete 24-h profiles without significant gaps were eligible for this analysis

Osc oscillometric device, ausc auscultatory device



**Fig. 1** Example of an ABPM profile in a child with marked systolic and diastolic hypertension. The dipping pattern is conserved (>10% difference between mean

daytime and mean nighttime BP). The systolic and diastolic load (percent of BP measurements above the 95th percentile) is 100%, respectively. *pct* percentile

Most ABPM software additionally provides BP hourly means, ambulatory arterial stiffness index (AASI), mean BP trend reports, and an output table for all BP and HR measurements including error readings and error codes. The ability to export raw data sets for further research analysis (e.g., Fourier analysis) is also of interest.

Table 2 provides a summary of the definitions of the most common ABPM parameters used in clinic and research.

First, for *clinical ABPM evaluation*, BP levels are assessed by comparing the mean SBP, DBP, and MAP values for daytime, nighttime, and 24 h with the respective sex- and height- or age-specific limits. BP values equal or above the 95th percentile are defined as hypertensive.

Then BP load, which is the percentage of valid BP readings above the 95th percentile, is determined. BP loads in excess of 25% are generally considered abnormal, with increased loads

associated with LVH (White et al. 1989a; Sorof et al. 2002a). The load can be assessed for the entire 24-h period or for the awake and asleep periods separately.

Third, nocturnal BP dipping is evaluated. Normal dipping is generally defined as a nocturnal decline of mean systolic and diastolic ambulatory BP level by at least 10%. The non-dipping phenomenon contributes to the overall renal and cardiovascular risk of an individual (Liu et al. 2003; Leung et al. 2006; Brotman et al. 2008). The cardiovascular mortality risk attributable to non-dipping is independent of the absolute 24-h blood pressure load (Ohkubo et al. 2002). Blunted nocturnal dipping has been associated with nephropathy in patients with type 1 (Lurbe et al. 2002) and 2 diabetes mellitus (Ettinger et al. 2005) and may be an early marker for impaired renal function.

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### Ambulatory Blood Pressure Monitoring Classification

A system for assigning stages to classify casual BP was introduced (JNC7 (Chobanian et al. 2003) and 4th Report (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004)) and a similar staging scheme was suggested for ambulatory BP levels in children including OBP, mean systolic ABPM, and the calculated BP load (Lurbe et al. 2004). This scheme was modified by the most recent update on ambulatory blood pressure monitoring in children and adolescents released by the American Heart Association (Flynn et al. 2014) (see Table 4).

However, this classification (Flynn et al. 2014) does not allow the categorization of patients with either office BP  $\geq$  95th percentile, normal mean ambulatory BP, and elevated BP loads or normal office BP ( $<$  90th percentile), normal mean ambulatory BP, but elevated ambulatory BP loads. In a retrospective study in more than 500 children by Lubrano, 14% of children evaluated according to this classification scheme did not fit in any category and 80% of prehypertensive children ended up in the uncategorized or the MH groups

(Lubrano et al. 2015). Also, almost 20% of pediatric CKD patients remained unclassified in the 4C Study (Cardiovascular Comorbidity in Children with Chronic Kidney Disease Study) using this classification (Schaefer et al. 2016). The prevalence of hypertension was influenced to a major degree by the consideration of elevated BP load. The prevalence of masked and confirmed hypertension more than doubled by defining patients with isolated high BP load as hypertensive (Schaefer et al. 2016). The inclusion of elevated BP load as a diagnostic criterion entirely explained the higher prevalence of ambulatory hypertension observed in the CKiD (Chronic Kidney Disease in Children) Study (Samuels et al. 2012) (58% in CKiD versus 26% in 4C).

In a recent meta-analysis of ten long-term outcome studies performed in more than 8000 adults, BP load did not contribute significantly to the cardiovascular risk associated with the mean 24-h BP level (Li et al. 2014) and was not included in the assessment of ambulatory hypertension in adults, which include fixed BP levels for the definition of hypertension (Pickering et al. 2005; Parati et al. 2014). There seems to be an obvious need to harmonize the diagnostic criteria of ambulatory hypertension in adults and children.

It is debatable, whether these unclassifiable children should be considered normotensive or masked hypertensive as suggested by the CKiD Study investigators (Mitsnefes et al. 2010; Samuels et al. 2012). Currently, the pediatric AHA Hypertension Guidelines recommend to approach such patients on a case-by-case basis, taking into account the presence or absence of underlying secondary causes of hypertension or specific cardiovascular risk factors (Flynn et al. 2014).

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### Role of Mean Arterial Pressure in the Evaluation of Ambulatory Blood Pressure Monitoring

The widely used oscillometric ABPM devices directly measure mean arterial pressure (MAP) and calculate SBP and DBP by manufacturer-specific software algorithms; as a result, SBP

**Table 4** Suggested staging scheme for ambulatory (or sustained) blood pressure levels in children

Blood pressure stage	Office BP <sup>a</sup>	Mean ambulatory SBP or DBP <sup>b</sup>	SBP or DBP load (%) <sup>c,d</sup>
Normal BP	<90th %tile	<95th %tile	<25
White coat hypertension	≥95th %tile	<95th %tile	<25
Prehypertension	≥90th %tile or >120/80 mmHg	<95th %tile	≥25
Masked hypertension	<95th %tile	≥95th %tile	≥25
Ambulatory hypertension	≥95th %tile	≥95th %tile	25–50
Severe ambulatory hypertension (at risk for end-organ damage)	≥95th %tile	≥95th %tile	>50

From Flynn et al. (Flynn et al. 2014) Reprinted with permission Hypertension. 2014;63:116–1135 copyright American Heart Association, Inc., modified from Lurbe et al. (2004)

BP blood pressure, SBP systolic BP, DBP diastolic BP, %tile percentile

<sup>a</sup>Based on the National High Blood Pressure Education Program data (4th Report)

<sup>b</sup>Based on normative ABPM values (Soergel et al. 1997; Wühl et al. 2002)

<sup>c</sup>For either the wake or the sleep period of the study, or both

<sup>d</sup>For patients with elevated load but normal mean ambulatory BP and office BP that is either normal (<90th %tile) or hypertensive (≥95th %tile), no specific ambulatory BP classification can be assigned based on current evidence and expert consensus. These “unclassified” patients should be evaluated on a case-by-case basis, taking into account the presence of secondary hypertension or multiple cardiovascular risk factors

and DBP values may significantly differ from SBP and DBP values obtained by auscultation (Smulyan and Safar 2011; Amoores 2012). Thus, it might be more appropriate to use MAP to classify the results of ABPM studies, because this is the BP parameter measured directly by oscillometric devices and the use of MAP parameters might simplify the definitions and staging of hypertension. MAP might be a more appropriate parameter for follow-up, especially for the analysis of intermediate and long-term outcomes of ABPM studies (Wühl et al. 2009).

### Calculation of Ambulatory Blood Pressure Monitoring Z-Scores or Percentile Data

The scientific application of pediatric ABPM reference data in parametric statistical procedures is compromised by the skewed distribution of BP in childhood. This problem has been largely solved by introduction of the LMS normalization method of Cole and Green (Cole and Green 1992), which transforms skewed BP values into normally distributed standard deviation scores (SDS) (Wühl et al. 2002). In brief, the LMS method describes the distribution of a measurement Y by its median

(M), the coefficient of variation (S), and a measure of skewness (L) required to transform the data to normality. Estimates for these parameters are obtained by applying a maximum-likelihood curve-fitting algorithm to the original data plotted over the independent variable of interest, in this case either age or height. The resulting estimates of L, M, and S can be used to construct percentiles ( $C_{\alpha}(t)$ ) by the equation:

$$C_{\alpha}(t) = M(t) \times [1 + L(t) \times S(t) \times z_{\alpha}]^{1/L(t)}$$
 where M(t), L(t), S(t), and  $C_{\alpha}(t)$  indicate the corresponding values of each parameter at age (or height) t.  $z_{\alpha}$  is the appropriate normal equivalent deviate (e.g., for  $\alpha = 97\%$ ,  $z_{\alpha} = 1.88$ ).

This equation can be rearranged to convert an individual child's BP value to an exact standard deviation score (SDS):

$$SDS = [(Y/M(t))^{L(t)} - 1]/(L(t) \times S(t))$$
 where Y is the child's individual systolic, diastolic, mean arterial BP, or heart rate value, and L(t), M(t) and S(t) are the gender-specific values of L, M, and S interpolated for the child's age or height.

Age-, gender-, and height-specific L, M, and S reference values for mean 24-h, daytime, and nighttime systolic, diastolic, and mean arterial pressure have been provided (Wühl et al. 2002) (Tables 5 and 6).

**Table 5** LMS reference values of mean 24-h, daytime, and nighttime systolic, diastolic, and mean arterial pressure relative to age and height in boys

Boys													
	N	Systolic BP									Diastolic BP		
		24 h			Day			Night			24 h		
		L	M	S	L	M	S	L	M	S	L	M	S
<b>Age</b>													
5.0	11	-2.205	104.6	0.058	-0.862	111.1	0.059	-1.929	95.0	0.062	-0.661	65.3	0.076
5.5	11	-2.066	105.1	0.059	-0.807	111.3	0.060	-1.793	95.3	0.065	-0.502	65.5	0.076
6.0	11	-1.927	105.5	0.060	-0.751	111.5	0.061	-1.658	95.5	0.067	-0.342	65.7	0.077
6.5	14	-1.786	105.9	0.061	-0.691	111.7	0.062	-1.522	95.8	0.070	-0.178	65.9	0.077
7.0	15	-1.646	106.3	0.062	-0.631	111.9	0.063	-1.386	96.1	0.073	-0.014	66.1	0.077
7.5	21	-1.503	106.6	0.063	-0.567	112.0	0.064	-1.251	96.4	0.076	0.144	66.2	0.077
8.0	22	-1.360	107.0	0.065	-0.503	112.2	0.065	-1.116	96.6	0.078	0.301	66.3	0.078
8.5	22	-1.220	107.4	0.066	-0.440	112.4	0.066	-0.984	97.0	0.080	0.441	66.4	0.078
9.0	21	-1.086	107.7	0.067	-0.381	112.6	0.067	-0.856	97.3	0.081	0.574	66.5	0.078
9.5	23	-0.968	108.2	0.068	-0.326	112.9	0.068	-0.733	97.7	0.082	0.688	66.5	0.079
10.0	19	-0.866	108.8	0.069	-0.276	113.4	0.069	-0.616	98.1	0.083	0.786	66.6	0.079
10.5	27	-0.783	109.6	0.069	-0.229	114.1	0.070	-0.503	98.7	0.084	0.865	66.7	0.079
11.0	25	-0.706	110.4	0.070	-0.177	114.9	0.071	-0.391	99.4	0.084	0.932	66.9	0.079
11.5	36	-0.627	111.5	0.071	-0.115	115.9	0.072	-0.280	100.2	0.084	0.981	67.0	0.080
12.0	27	-0.540	112.6	0.072	-0.041	117.0	0.072	-0.171	101.2	0.084	1.017	67.2	0.080
12.5	35	-0.441	113.8	0.072	0.041	118.2	0.073	-0.065	102.2	0.084	1.040	67.3	0.080
13.0	21	-0.324	115.1	0.072	0.132	119.5	0.073	0.040	103.4	0.084	1.050	67.4	0.080
13.5	30	-0.181	116.4	0.073	0.235	120.9	0.073	0.144	104.6	0.083	1.047	67.6	0.080
14.0	16	-0.018	117.8	0.073	0.348	122.3	0.073	0.248	105.8	0.083	1.036	67.7	0.080
14.5	19	0.157	119.2	0.073	0.469	123.8	0.073	0.349	107.1	0.082	1.019	67.9	0.079
15.0	11	0.338	120.6	0.072	0.595	125.3	0.073	0.448	108.3	0.082	1.000	68.1	0.079
15.5	9	0.522	122.0	0.072	0.723	126.8	0.073	0.545	109.6	0.081	0.980	68.4	0.079
16.0	18	0.706	123.4	0.072	0.851	128.2	0.073	0.641	110.9	0.080	0.959	68.6	0.079
<b>Height</b>													
120	31	-1.123	104.5	0.063	-1.291	110.8	0.069	-0.053	93.6	0.077	-1.177	65.6	0.087
125	25	-0.991	105.3	0.064	-1.007	111.1	0.069	-0.314	94.6	0.079	-0.957	65.9	0.087
130	25	-0.856	106.2	0.065	-0.710	111.5	0.069	-0.570	95.6	0.080	-0.733	66.1	0.087
135	44	-0.709	107.2	0.066	-0.380	112.0	0.068	-0.807	96.7	0.081	-0.511	66.4	0.086
140	50	-0.556	108.3	0.066	-0.075	112.7	0.067	-0.997	97.9	0.082	-0.322	66.6	0.086
145	48	-0.406	109.5	0.067	0.117	113.7	0.067	-1.106	99.0	0.082	-0.183	66.9	0.085
150	43	-0.275	110.9	0.067	0.125	115.1	0.067	-1.126	100.1	0.081	-0.107	67.1	0.084
155	32	-0.155	112.5	0.067	-0.031	116.8	0.066	-1.068	101.3	0.081	-0.110	67.2	0.083
160	39	-0.017	114.2	0.067	-0.251	118.6	0.067	-0.948	102.6	0.080	-0.189	67.3	0.083
165	29	0.154	116.1	0.066	-0.431	120.6	0.068	-0.795	104.1	0.079	-0.324	67.5	0.082
170	28	0.378	118.0	0.066	-0.463	122.6	0.069	-0.626	105.6	0.079	-0.479	67.6	0.081
175	31	0.651	119.7	0.064	-0.373	124.4	0.069	-0.451	107.2	0.078	-0.635	67.8	0.080
180	20	0.942	121.5	0.063	-0.244	126.2	0.069	-0.277	108.7	0.078	-0.785	68.0	0.078
185	19	1.240	123.2	0.061	-0.098	128.0	0.069	-0.100	110.2	0.078	-0.932	68.2	0.077

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									MAP						
Day			Night			24 h			Day			Night			
L	M	S	L	M	S	L	M	S	L	M	S	L	M	S	
1.477	72.1	0.075	-2.245	55.0	0.086	-2.063	76.9	0.071	-0.132	83.5	0.069	-2.191	66.7	0.078	
1.505	72.2	0.076	-2.065	55.1	0.089	-1.918	77.4	0.071	-0.069	83.8	0.070	-2.074	67.2	0.079	
1.533	72.4	0.077	-1.884	55.3	0.092	-1.772	77.9	0.071	-0.007	84.1	0.071	-1.955	67.7	0.081	
1.558	72.4	0.078	-1.702	55.4	0.095	-1.610	78.3	0.071	0.060	84.3	0.072	-1.826	68.1	0.082	
1.583	72.5	0.079	-1.520	55.5	0.098	-1.447	78.7	0.071	0.127	84.5	0.073	-1.696	68.6	0.084	
1.599	72.5	0.080	-1.338	55.6	0.100	-1.262	79.0	0.072	0.199	84.7	0.074	-1.544	68.9	0.085	
1.614	72.5	0.081	-1.155	55.7	0.102	-1.078	79.3	0.072	0.272	84.8	0.076	-1.393	69.2	0.086	
1.620	72.4	0.082	-0.982	55.7	0.104	-0.870	79.5	0.073	0.353	84.8	0.077	-1.220	69.5	0.087	
1.622	72.3	0.083	-0.813	55.8	0.105	-0.651	79.7	0.073	0.442	84.9	0.078	-1.040	69.7	0.088	
1.621	72.1	0.083	-0.655	55.8	0.105	-0.409	79.9	0.074	0.552	84.9	0.078	-0.843	69.8	0.089	
1.614	72.1	0.083	-0.505	55.8	0.106	-0.146	80.2	0.075	0.682	85.0	0.079	-0.631	70.0	0.090	
1.598	72.0	0.083	-0.365	55.8	0.106	0.139	80.5	0.075	0.832	85.1	0.079	-0.398	70.2	0.090	
1.576	72.0	0.083	-0.229	55.9	0.105	0.443	80.8	0.076	0.998	85.3	0.080	-0.147	70.5	0.091	
1.544	72.0	0.083	-0.097	55.9	0.105	0.774	81.2	0.077	1.183	85.6	0.080	0.133	70.8	0.091	
1.505	72.0	0.083	0.031	56.0	0.104	1.119	81.7	0.077	1.378	85.9	0.081	0.437	71.2	0.091	
1.460	72.1	0.083	0.154	56.1	0.104	1.470	82.1	0.078	1.569	86.3	0.081	0.761	71.6	0.090	
1.407	72.2	0.083	0.270	56.3	0.104	1.822	82.7	0.078	1.755	86.8	0.082	1.097	72.1	0.089	
1.347	72.3	0.083	0.378	56.4	0.103	2.173	83.2	0.078	1.937	87.4	0.082	1.436	72.6	0.088	
1.279	72.5	0.082	0.483	56.5	0.102	2.525	83.8	0.078	2.117	88.0	0.083	1.777	73.1	0.086	
1.203	72.7	0.082	0.588	56.7	0.101	2.874	84.4	0.078	2.291	88.7	0.083	2.122	73.6	0.084	
1.123	73.0	0.082	0.694	56.8	0.100	3.222	85.1	0.078	2.464	89.4	0.083	2.469	74.0	0.082	
1.040	73.2	0.083	0.801	57.0	0.099	3.571	85.7	0.077	2.635	90.1	0.084	2.816	74.5	0.080	
0.957	73.5	0.083	0.908	57.1	0.098	3.919	86.4	0.077	2.806	90.8	0.084	3.164	74.9	0.077	
1.345	72.3	0.087	0.440	54.3	0.089	-1.747	77.5	0.076	0.135	83.8	0.081	-2.736	66.8	0.084	
1.436	72.3	0.086	0.430	54.8	0.092	-1.352	78.1	0.076	0.368	84.1	0.080	-2.305	67.6	0.085	
1.531	72.2	0.086	0.421	55.1	0.095	-0.951	78.7	0.076	0.604	84.3	0.079	-1.867	68.3	0.086	
1.629	72.1	0.085	0.410	55.5	0.098	-0.547	79.3	0.076	0.844	84.5	0.078	-1.411	69.0	0.087	
1.711	72.1	0.083	0.398	55.8	0.100	-0.148	79.9	0.075	1.083	84.7	0.077	-0.932	69.6	0.087	
1.763	72.1	0.082	0.391	56.0	0.101	0.235	80.5	0.076	1.309	85.0	0.076	-0.427	70.1	0.087	
1.777	72.1	0.081	0.395	56.2	0.101	0.589	81.1	0.076	1.509	85.4	0.076	0.092	70.6	0.087	
1.740	72.1	0.080	0.413	56.2	0.101	0.914	81.7	0.076	1.680	85.8	0.076	0.620	71.2	0.086	
1.650	72.2	0.081	0.442	56.3	0.100	1.217	82.3	0.077	1.829	86.4	0.076	1.159	71.9	0.085	
1.509	72.3	0.081	0.487	56.5	0.099	1.509	83.1	0.077	1.963	87.1	0.078	1.706	72.7	0.084	
1.329	72.6	0.082	0.556	56.7	0.097	1.805	83.9	0.077	2.092	88.0	0.080	2.269	73.6	0.082	
1.136	72.8	0.082	0.647	56.9	0.096	2.110	84.7	0.078	2.226	89.0	0.082	2.843	74.5	0.080	
0.939	73.1	0.083	0.755	57.1	0.094	2.423	85.5	0.078	2.364	90.0	0.084	3.425	75.4	0.078	
0.741	73.4	0.083	0.871	57.3	0.093	2.737	86.3	0.079	2.503	91.0	0.087	4.010	76.2	0.075	

**Table 6** LMS reference values of mean 24-h, daytime, and nighttime systolic, diastolic, and mean arterial pressure relative to age and height in girls

Girls													
	N	Systolic BP									Diastolic BP		
		24 h			Day			Night			24 h		
		L	M	S	L	M	S	L	M	S	L	M	S
<b>Age</b>													
5.0	14	1.362	102.8	0.073	2.507	108.4	0.077	0.144	94.8	0.082	0.646	65.5	0.078
5.5	15	1.174	103.4	0.073	2.274	109.0	0.075	0.052	95.2	0.082	0.773	65.5	0.078
6.0	15	0.987	104.1	0.072	2.041	109.5	0.074	-0.040	95.6	0.083	0.900	65.6	0.078
6.5	17	0.811	104.7	0.071	1.819	110.1	0.073	-0.123	95.9	0.083	1.025	65.7	0.078
7.0	17	0.648	105.3	0.070	1.610	110.6	0.073	-0.194	96.2	0.083	1.148	65.8	0.078
7.5	13	0.503	105.9	0.069	1.417	111.1	0.072	-0.250	96.5	0.084	1.269	65.8	0.079
8.0	12	0.378	106.5	0.069	1.244	111.5	0.071	-0.286	96.8	0.084	1.388	65.9	0.079
8.5	12	0.278	107.0	0.068	1.096	111.9	0.070	-0.298	97.2	0.084	1.503	65.9	0.080
9.0	12	0.199	107.6	0.067	0.969	112.4	0.070	-0.289	97.5	0.084	1.611	66.0	0.080
9.5	22	0.154	108.2	0.066	0.874	112.8	0.069	-0.253	97.9	0.084	1.701	66.1	0.081
10.0	20	0.134	108.7	0.066	0.805	113.3	0.069	-0.197	98.2	0.084	1.775	66.2	0.082
10.5	37	0.151	109.2	0.066	0.775	113.7	0.068	-0.116	98.6	0.084	1.819	66.3	0.083
11.0	31	0.201	109.7	0.065	0.780	114.2	0.068	-0.015	99.0	0.083	1.832	66.4	0.084
11.5	35	0.280	110.2	0.065	0.819	114.7	0.068	0.106	99.3	0.082	1.811	66.5	0.085
12.0	31	0.378	110.7	0.065	0.878	115.3	0.068	0.241	99.7	0.081	1.757	66.6	0.086
12.5	37	0.485	111.3	0.065	0.945	115.8	0.068	0.389	100.1	0.079	1.675	66.8	0.086
13.0	27	0.599	111.8	0.064	1.020	116.4	0.067	0.549	100.5	0.078	1.571	67.0	0.086
13.5	30	0.722	112.3	0.064	1.107	117.0	0.066	0.720	100.9	0.076	1.453	67.1	0.086
14.0	20	0.854	112.8	0.063	1.207	117.5	0.065	0.898	101.3	0.074	1.328	67.2	0.085
14.5	24	0.991	113.3	0.062	1.319	118.1	0.063	1.083	101.6	0.072	1.202	67.4	0.084
15.0	16	1.129	113.8	0.061	1.435	118.6	0.062	1.269	102.0	0.069	1.075	67.5	0.082
15.5	12	1.265	114.3	0.059	1.552	119.1	0.061	1.454	102.5	0.067	0.946	67.6	0.081
16.0	16	1.400	114.8	0.058	1.668	119.6	0.059	1.639	102.9	0.065	0.816	67.7	0.080
<b>Height</b>													
120	30	0.593	104.0	0.059	2.107	110.0	0.061	1.565	95.0	0.070	2.996	65.9	0.065
125	32	0.553	105.0	0.060	1.947	110.5	0.062	1.184	95.7	0.071	2.790	65.9	0.070
130	27	0.535	106.0	0.060	1.804	111.0	0.063	0.823	96.4	0.073	2.592	66.0	0.075
135	20	0.566	106.8	0.061	1.686	111.6	0.064	0.518	96.9	0.075	2.407	66.1	0.080
140	34	0.657	107.6	0.062	1.583	112.2	0.065	0.292	97.5	0.077	2.221	66.2	0.084
145	39	0.797	108.7	0.062	1.480	113.1	0.066	0.167	98.1	0.079	2.006	66.3	0.087
150	54	0.973	109.9	0.063	1.367	114.3	0.066	0.186	98.9	0.080	1.743	66.5	0.089
155	51	1.194	111.2	0.062	1.259	115.6	0.066	0.378	100.0	0.079	1.435	66.7	0.087
160	65	1.485	112.4	0.060	1.220	117.0	0.064	0.745	101.1	0.077	1.088	67.0	0.083
165	53	1.834	113.7	0.058	1.261	118.3	0.060	1.272	102.2	0.073	0.700	67.4	0.078
170	46	2.210	115.0	0.055	1.332	119.8	0.055	1.903	103.4	0.070	0.285	68.0	0.071
175	24	2.601	116.4	0.052	1.410	121.2	0.050	2.579	104.6	0.068	-0.136	68.6	0.064

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						MAP								
Day			Night			24 h			Day			Night		
L	M	S	L	M	S	L	M	S	L	M	S	L	M	S
1.670	72.6	0.085	0.122	56.4	0.120	0.487	77.2	0.070	1.277	83.7	0.080	0.507	68.7	0.090
1.717	72.6	0.085	0.120	56.2	0.120	0.675	77.5	0.070	1.371	83.8	0.079	0.528	68.8	0.090
1.765	72.6	0.085	0.119	55.9	0.119	0.864	77.8	0.070	1.465	83.9	0.079	0.549	68.8	0.091
1.813	72.5	0.085	0.123	55.7	0.119	1.051	78.0	0.070	1.560	84.0	0.078	0.579	68.8	0.092
1.861	72.4	0.085	0.129	55.5	0.119	1.239	78.2	0.071	1.656	84.0	0.078	0.617	68.8	0.092
1.911	72.3	0.086	0.137	55.3	0.120	1.427	78.4	0.071	1.755	84.1	0.077	0.662	68.8	0.093
1.962	72.2	0.086	0.142	55.1	0.120	1.618	78.6	0.071	1.857	84.1	0.077	0.711	68.8	0.094
2.015	72.1	0.086	0.143	54.9	0.120	1.811	78.8	0.071	1.961	84.1	0.077	0.765	68.9	0.095
2.066	72.0	0.086	0.141	54.8	0.121	2.001	79.0	0.071	2.066	84.2	0.076	0.824	68.9	0.095
2.109	71.9	0.087	0.135	54.7	0.121	2.181	79.2	0.071	2.171	84.3	0.076	0.893	69.0	0.096
2.146	71.8	0.087	0.125	54.6	0.121	2.352	79.4	0.071	2.274	84.4	0.076	0.970	69.1	0.096
2.175	71.8	0.087	0.112	54.5	0.121	2.506	79.6	0.072	2.375	84.5	0.076	1.059	69.2	0.097
2.195	71.8	0.087	0.096	54.3	0.121	2.640	79.9	0.072	2.474	84.7	0.076	1.160	69.3	0.097
2.207	71.9	0.088	0.074	54.2	0.120	2.749	80.2	0.073	2.570	84.9	0.076	1.274	69.4	0.097
2.210	72.1	0.087	0.043	54.2	0.119	2.836	80.5	0.073	2.663	85.2	0.076	1.399	69.6	0.097
2.203	72.2	0.087	0.001	54.2	0.117	2.902	80.9	0.074	2.753	85.5	0.076	1.534	69.8	0.096
2.192	72.4	0.087	-0.051	54.3	0.115	2.957	81.2	0.074	2.843	85.9	0.077	1.676	70.1	0.095
2.179	72.6	0.085	-0.110	54.4	0.112	3.008	81.5	0.074	2.933	86.2	0.076	1.825	70.3	0.094
2.169	72.8	0.084	-0.174	54.5	0.109	3.061	81.9	0.074	3.026	86.5	0.076	1.977	70.6	0.093
2.162	73.0	0.082	-0.243	54.7	0.106	3.121	82.2	0.073	3.122	86.8	0.076	2.132	70.9	0.092
2.158	73.2	0.080	-0.316	54.9	0.102	3.183	82.4	0.073	3.219	87.1	0.076	2.287	71.2	0.090
2.153	73.3	0.078	-0.391	55.1	0.099	3.243	82.7	0.072	3.317	87.4	0.075	2.440	71.5	0.089
2.148	73.5	0.076	-0.467	55.3	0.096	3.302	83.0	0.072	3.415	87.7	0.075	2.593	71.8	0.088
1.952	73.2	0.077	1.491	55.4	0.112	1.848	77.2	0.067	2.092	83.3	0.074	0.335	68.0	0.097
1.915	72.8	0.080	1.276	55.3	0.115	1.976	77.8	0.068	2.039	83.7	0.076	0.410	68.2	0.096
1.881	72.4	0.083	1.075	55.1	0.118	2.103	78.3	0.069	2.014	84.0	0.077	0.477	68.4	0.096
1.851	72.1	0.087	0.891	54.8	0.120	2.236	78.7	0.071	2.032	84.1	0.079	0.553	68.5	0.096
1.832	71.8	0.090	0.705	54.6	0.121	2.366	79.2	0.073	2.099	84.3	0.080	0.650	68.7	0.097
1.828	71.7	0.092	0.497	54.4	0.121	2.479	79.7	0.074	2.217	84.5	0.080	0.778	69.0	0.097
1.836	71.8	0.092	0.279	54.3	0.118	2.591	80.2	0.074	2.404	84.9	0.079	0.955	69.3	0.097
1.846	72.0	0.090	0.074	54.3	0.114	2.751	80.8	0.073	2.684	85.5	0.077	1.202	69.8	0.095
1.835	72.4	0.085	-0.091	54.6	0.110	2.967	81.5	0.072	3.042	86.2	0.074	1.514	70.4	0.093
1.799	73.1	0.077	-0.200	54.9	0.106	3.214	82.3	0.069	3.442	87.0	0.070	1.871	71.2	0.091
1.739	73.9	0.069	-0.261	55.1	0.147	3.466	83.1	0.066	3.852	88.0	0.064	2.249	72.0	0.089
1.671	74.8	0.061	-0.296	55.4	0.099	3.728	84.0	0.064	4.268	88.9	0.059	2.638	72.8	0.087



## Blood Pressure Variability

ABPM provides information not only on daytime and nighttime blood pressure patterns but also on BP *variability*. Linear analyses, such as dividing the 24-h period into day and night intervals, either arbitrarily or according to a patient diary, allow a quantification of the nocturnal BP fall, or “dipping,” both in absolute and relative terms. Alternative methods include the calculation of cumulative sums (Stanton et al. 1992), chronobiological cosinor analysis (Halberg et al. 1972), and Fourier analysis, which is the simultaneous application of several cosine functions (Staessen et al. 1993).

Even though definitions of “non-dipping” vary, the prognostic relevance of the non-dipping phenomenon has been demonstrated in adults with renal failure (Liu et al. 2003) and in the general population (Ohkubo et al. 2002). Controversy persists about the physiological basis of circadian and ultradian BP rhythms. While evidence from shift workers suggests that BP rhythms are determined largely externally by physical activity, the fact that disturbances of the diurnal BP pattern are found in a variety of pathological conditions has led to the suggestion that an endogenous rhythm of autonomic nervous activity is at least partly responsible for the generation of circadian BP rhythmicity.

*Fourier analysis* appears to be superior to linear analysis because there is no need to define day and night intervals, which presuppose an activity-related origin of BP variations. The combination of several rhythms allows a more detailed and flexible description of the 24-h period than the original cosinor method.

Circadian cardiovascular rhythmicity is present in the majority of healthy children and adolescents with an attenuation of 24-h heart rate periodicity during puberty. In addition, ultradian rhythms are found in the majority of healthy children, with an age-related shift from 8-h towards 6-h or 12-h predominant rhythmicity (Hadtstein et al. 2004). Compared to pediatric reference data (Hadtstein et al. 2004), children with chronic kidney disease show marked blunting and delay of the rhythmicity of both BP and heart rate (Wühl

et al. 2005). Changes in ultradian and circadian rhythms were independent of each other. Also, the ultradian BP amplitudes but not the circadian amplitudes or conventional dipping parameters were correlated to indices of renal function, raising the possibility that ultradian rhythms play an independent role in chronic kidney disease. Current evidence suggests that, whereas normal circadian BP variation is a positive predictor of cardiovascular outcome, ultradian BP variability is more associated with disease states (Litwin et al. 2010; Wolfenstetter et al. 2012; Saner et al. 2016). Increased BP variability has been also demonstrated in obese children and is most likely related to increased sympathetic nervous system activation in obesity-related hypertension (Sorof et al. 2002b). In adults, greater BP variability has been correlated with the development of hypertensive left ventricular hypertrophy (Parati et al. 2006).

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## Reproducibility of Ambulatory Blood Pressure Monitoring

One of the key advantages of ABPM is its superior reproducibility in comparison to casual BP measurements, demonstrated in adults (Ward and Hansen 1984; Palatini et al. 1994; van der Steen et al. 1999) and children (Gimpel et al. 2009). Excellent reproducibility has also been shown for the nocturnal dipping phenomenon (Zakopoulos et al. 2001). Still, a certain degree of BP variability will be found even with ABPM; in children with borderline hypertension, more than one ABPM may be required to judge the consistence of elevated blood pressure (Rucki and Feber 2001).

In view of the numerous ethical and practical challenges associated with the enrollment of children in randomized, controlled antihypertensive drug trials, the superior sensitivity of ABPM in detecting treatment-induced BP changes provides a strong argument in favor of using this methodology to define primary endpoints in clinical trials (Gimpel et al. 2009).

Also, in the serial evaluation of blood pressure control in children receiving antihypertensive

treatment, the superior consistency of ABPM provides valuable qualitative and quantitative information, which is highly likely to improve blood pressure control and long-term cardiovascular outcomes.

## Conclusion

With its wide availability, proven technical feasibility across the pediatric age range, availability of pediatric reference data, and superior sensitivity in diagnosing hypertension and detecting pharmacological treatment effects, ABPM should be considered the method of choice for diagnosis and follow-up in pediatric hypertension.

However, there are still some open issues concerning normative data sets in infants and younger children and in different ethnicities, optimization of protocols for monitoring BP, and data analysis, and appropriate validation of devices for use in the pediatric population.

## Cross-References

- [The Role of ABPM in Evaluation of Hypertensive Target-Organ Damage](#)

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# Methodology and Applicability of Home Blood Pressure Monitoring in Children and Adolescents

17

George S. Stergiou and Angeliki Ntineri

## Abstract

Accumulating evidence suggests that in children and adolescents, home blood pressure (BP) monitoring is useful for out-of-office BP evaluation. Home BP monitoring has advantages similar to ambulatory monitoring, by offering multiple measurements in the individual's usual environment, which avoid the white-coat and masked hypertension phenomena and are more reproducible than the conventional office measurements. Home BP appears to have similar diagnostic value in children as in adults and might be a useful alternative to ambulatory monitoring in detecting white-coat and masked hypertension. In children and adolescents, home BP is lower than daytime ambulatory BP (in contrast to adults who have similar levels) and is higher than office BP in younger children but with progressive elimination of the latter difference with increasing age. Home BP monitoring is feasible in most children and has relatively low cost. Obtaining duplicate, morning and evening, BP measurements for 6–7 days is currently recommended for optimal home BP assessment, with a minimum of 3 days

considered acceptable. Electronic arm-cuff devices which have been validated specifically in children should be used with the appropriate sized cuff. Normalcy data for home BP in children have been provided by a school-based study. Data on its relationship with target-organ damage are scarce, yet promising. Home BP monitoring has considerable potential for improving the care of children with hypertension.

## Keywords

Adolescents • Children • Home blood pressure • Masked hypertension • Self-measurement • White-coat hypertension

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## Introduction

Although conventional blood pressure (BP) measurement in a physician's office remains the basis for the evaluation of hypertension in adults and in children, it is well recognized that it frequently leads to incorrect diagnosis, mainly due to the white-coat and masked hypertension phenomena (Flynn et al. 2014; Lurbe et al. 2005; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004; O'Brien et al. 2013; Stergiou et al. 2004b, 2005b). Thus, it is currently recommended that the diagnosis of hypertension in children not be based solely on office BP measurements. Documentation of elevated BP out of the office is needed to confirm the diagnosis of hypertension, mainly using ambulatory BP monitoring (Flynn et al. 2014, 2017; Lurbe et al. 2016; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004).

In adults, both ambulatory (O'Brien et al. 2013; Piper et al. 2015) and home BP monitoring (Parati et al. 2008; Pickering et al. 2008) are recognized as important methods for hypertension management. However, in children, although the usefulness of ambulatory monitoring is well established (Flynn et al. 2014, 2017; Lurbe et al. 2016; O'Brien et al. 2005; Urbina et al. 2008), the potential of home BP monitoring in the evaluation of hypertension remains largely unrecognized and unexplored (Stergiou et al. 2009a). American guidelines for pediatric hypertension (Flynn et al. 2017; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004) provide very little or no guidance on home BP monitoring, because of the limited evidence on its clinical usefulness in children. However, the 2009 European Society of Hypertension

guidelines for pediatric hypertension (Lurbe et al. 2009) do include a section on home BP monitoring, which was further expanded in the 2016 revised guidelines (Lurbe et al. 2016) as a result of the accumulating evidence on the applicability of this method in children.

It is important to mention that home BP monitoring is already being used in children as a part of routine clinical practice, as shown by surveys in the USA, Canada, and Germany, which report that more than 70% of pediatric nephrologists utilize home BP monitoring in children with hypertension or renal disease, and 64% of them consider home measurements more important than office measurements (Bald and Hoyer 2001; Woroniecki and Flynn 2005).

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## Advantages-Disadvantages

### Advantages

Home BP monitoring has several important advantages compared to conventional office measurements and in some respects also to ambulatory monitoring (Table 1). As is the case with ambulatory BP monitoring, home monitoring is advantageous over office measurements, as it provides more detailed information on BP behavior by obtaining multiple readings compared to only two or three office measurements. In addition, these measurements are taken away from the potentially stressful office setting and in the usual environment of the child. Thus, home BP is free from the white-coat and masked hypertension phenomena, which are major pitfalls of conventional office BP (Parati and Stergiou 2003; Parati et al. 2008; Stergiou et al. 2014). An important difference between home and ambulatory BP monitoring is that with the former readings are obtained over a period of several days, weeks, or even months, and always at home, whereas with the latter BP readings are crowded into 24 h. Ambulatory BP monitoring, however, obtains readings at school and during sleep which are not typically captured by home BP monitoring. Home BP has been shown to have similar reproducibility to ambulatory BP, which is superior to



**Table 1** Advantages of home blood pressure measurements

Evidence in adults	Evidence in children
<b>Advantages of home BP compared to office BP</b>	
Multiple measurements in several days, weeks or months and in usual environment	Lurbe et al. (2016)
Free of white-coat and masked hypertension phenomena	Stergiou et al. (2008b, 2009c) and Furusawa et al. (2011)
Superior reproducibility – improves power of clinical trials	Stergiou et al. (2005a, 2009b)
Devoid of observer error and bias	Parati et al. (2008)
Devoid of placebo effect	NA
Feasible for wide application in clinical practice	Salgado et al. (2011), Stergiou et al. (2007, 2008b) and Wühl et al. (2004)
Improve long-term compliance with anti-hypertensive drug therapy	NA
Improve hypertension control rates	NA
More cost-effective	NA
<b>Advantages of home BP compared to ambulatory BP</b>	
More widely available	Parati et al. (2008), Bald and Hoyer (2001), and Woroniecki and Flynn (2005)
Preferred by users	NA
Less discomfort and minimal restriction of daily activities and sleep	NA
Less costly	NA

BP blood pressure, NA not available

that of office BP (Stergiou et al. 2005a, 2009b). It has been shown that in clinical research the higher reproducibility of home BP increases the statistical power of clinical trials, which allows the inclusion of a smaller sample size than needed when using office BP measurements (Stergiou et al. 2002). In addition, home BP appears to have similar diagnostic ability as ambulatory BP, with the observed diagnostic disagreement between the two methods mainly due to the imperfect reproducibility of the two methods – although for both methods this is superior to office measurements (Stergiou and Ntineri 2015).

When home BP is monitored using an automated electronic device – which is usually the case and the recommended technique – the intra- and interobserver error (including the terminal digit preference, usually 5 or 0) and the observer prejudice and bias (the observer adjusts the recorded BP according to his/her expectations), which are known drawbacks of auscultatory office BP measurements, are all avoided, as it is also the case with ambulatory BP monitoring (Karpettas et al. 2013; Rose 1965). Home and ambulatory BP monitoring are also devoid of the placebo effect, which limits the reliability of office BP measurements to accurately quantify treatment-induced BP changes in clinical research and in practice (Vaur et al. 1998; Redwine et al. 2012).

From a practical point of view, home BP monitoring is well accepted by adult users. As it entails less discomfort and minimal restrictions on daily activities and sleep, it is preferred to ambulatory monitoring by most patients (Little et al. 2002; Nasothimiou et al. 2014). Studies in adults have shown that home BP monitoring can improve hypertension control rates by improving patients' long-term compliance with antihypertensive drug treatment (Cappuccio et al. 2004; Ogedegbe and Schoenthaler 2006). In addition, it should be mentioned that home BP monitoring has lower cost than ambulatory monitoring, and studies in adults have shown that it is a cost-effective method for long-term BP monitoring (Arrieta et al. 2014; Boubouchairopoulou et al. 2014).

## Disadvantages

The primary limitation of home BP monitoring in children is that the evidence on its clinical implementation and relevance is still limited compared to that for ambulatory monitoring, yet several relevant studies have been published in the last decade (Stergiou et al. 2009a). Another important concern is the potential for reporting bias with over- or underreporting of home BP readings. This can be prevented by using devices with automated memory or PC-link capacity or with home BP telemonitoring (Myers and Stergiou 2014).

Another important consideration regarding home BP monitoring is that electronic BP monitors that have been successfully validated in adults might not be accurate in children (Chiolero et al. 2014). Thus, children are regarded as a special group for BP monitor validation requiring separate validation studies (American National Standards Institute, Association for the Advancement of Medical Instrumentation and International Organization for Standardization 2013; O'Brien et al. 1993, 2010). Unfortunately, at the present time there is scarce evidence on the accuracy of electronic BP monitors in children, with very few devices successfully tested for measurement accuracy using an established protocol in this population. In addition, there is limited availability of varying cuff sizes for the existing validated monitors, which are necessary to fit the wide range of arm sizes in the pediatric population.

One final limitation is that home BP monitoring might induce anxiety in some children or parents. Careful training and medical supervision are required in order to obtain reliable BP measurements and feel comfortable with the process of home monitoring.

The only clear disadvantage of home BP monitoring compared to ambulatory monitoring is that the latter allows the evaluation of BP during nighttime sleep, which is important particularly in children with diabetes, kidney disease, or sleep apnea. Some novel home monitors allow reliable nocturnal BP evaluation and the detection of non-dippers (Hosohata et al. 2007; Stergiou et al. 2012) yet to date these have not been studied in children (Table 2).

**Table 2** Disadvantages of home blood pressure monitoring compared to office measurements and ambulatory monitoring

Scarce evidence on clinical relevance
Few electronic home monitors validated specifically in children
Limited availability of cuff sizes for children
Reporting bias of home measurements
Potential to induce anxiety and excessive monitoring
Need for training (minimal with automated devices)
Inability to monitor blood pressure during nighttime sleep

## Methodology

### Comparison of BP Measurement Methods

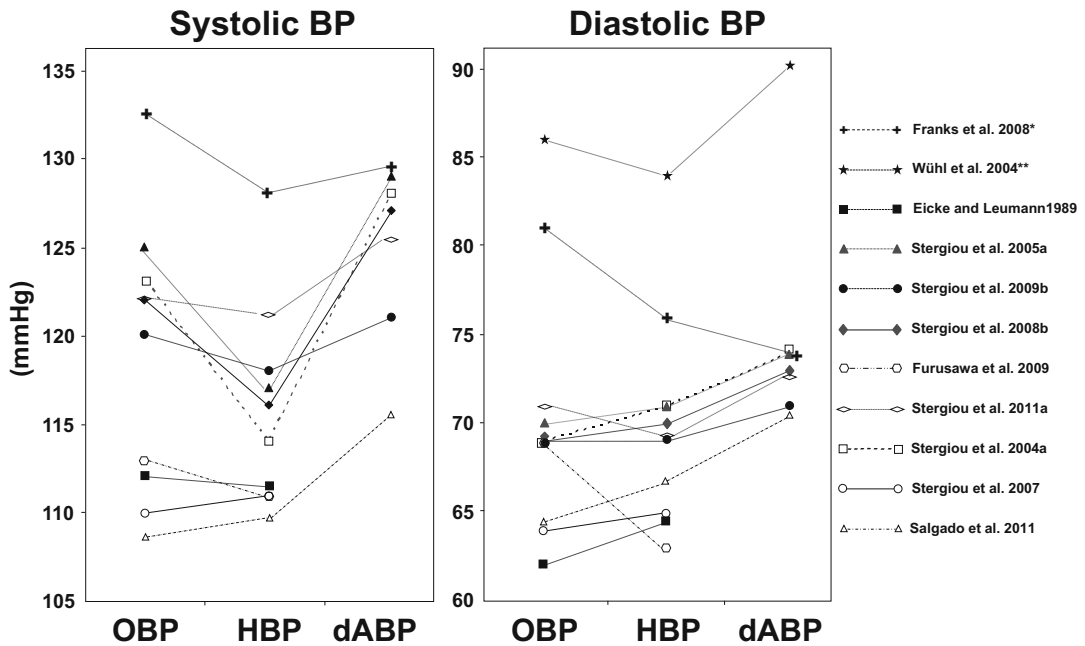
#### Home Versus Office BP

Most studies comparing home with office BP in children and adolescents have shown that, as in adults, systolic home BP is lower than office BP in subjects with hypertension (Franks et al. 2008; Stergiou et al. 2004a, b, 2005a, b, 2008b, 2009b; Wühl et al. 2004), whereas there is little difference in normotensives (Eicke and Leumann 1989; Stergiou et al. 2007). Regarding the diastolic BP values, there appears to be no difference between home and office BP readings in both hypertensive and normotensive children and adolescents (Stergiou et al. 2009a; Fig. 1).

#### Home Versus Ambulatory BP

In contrast to data in adults in whom home BP values are similar to those of daytime ambulatory BP, studies in children and adolescents have shown systolic home BP (and less so diastolic BP) to be lower than daytime ambulatory BP (Stergiou et al. 2004a, 2005a, 2008b, 2009a, 2011a; Fig. 1). This disparity is probably attributed to the higher level of physical activity during the day in the younger population, whereas most adults have a rather sedentary lifestyle. In a study of 102 untreated children and adolescents referred to a hypertension center for elevated BP (48% without hypertension), systolic home BP was shown to be lower than daytime ambulatory BP by an average of 11 mmHg and diastolic BP by 3 mmHg (Stergiou et al. 2008b).

This relationship is also present in children with chronic renal failure as shown in the ESCAPE (Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of Chronic Renal Failure in Pediatric Patients) trial, where mean arterial home BP was lower than daytime ambulatory BP by 6.4 mmHg (Wühl et al. 2004). Thus, in children, although home and ambulatory BP share major similarities, they also have important differences as they evaluate different aspects of the individual's BP behavior and profile and



**Fig. 1** Studies in children and adolescents comparing home blood pressure versus daytime ambulatory and office blood pressure measurements. (Adapted from Stergiou

et al. (2009a)). *BP* blood pressure, *OBP* office BP, *dABP* daytime ambulatory BP, *HBP* home BP, \* only average 24-h BP reported, \*\* only mean arterial BP reported

should be regarded as complementary methods, rather than competitive or interchangeable.

**Impact of Age on Differences Between BP Measurement Methods**

In children and adolescents, the relationship between office, home, and ambulatory BP is not the same in all the age subgroups. The Arsakeion school study evaluated 765 young healthy individuals. Among the younger subjects (aged 6–12 years), home BP was higher than office BP, whereas in the adolescents ( $\geq 12$  years) this difference was eliminated (Stergiou et al. 2008c). Both measurement methods were obtained using the same automated electronic device, which excludes any influence due to different BP measurement technology (e.g., auscultatory for office versus automated for home BP) (Stergiou et al. 2008c, 2011b). This change between younger and older subjects in the home-office BP difference might be due to the fact that children of different age may be affected differently by the office environment (Stergiou et al. 2008c, 2011b). Thus, the

white-coat effect, which is considered an alert reaction specific to the office setting, might be more prominent in adolescents, resulting in higher office than out-of-office BP levels with increasing age. Indeed, the difference between the two out-of-office BP measurements (home and ambulatory) does not appear to change with aging in children and adolescents (Stergiou et al. 2011b).

Another study assessed the differences among clinic, home, and ambulatory blood pressure with increasing age in 642 untreated subjects referred to a hypertension clinic, of whom 177 were children and adolescents (Stergiou et al. 2015). Systolic daytime ambulatory BP was higher than office and home BP in both children and adolescents. Moreover, home BP was higher than office BP in children but not in adolescents. Regarding diastolic BP, daytime ambulatory BP was higher than home BP in both children and adolescents, whereas office BP was lower than daytime ambulatory BP in children and higher than home BP in adolescents. No differences were detected between office and home BP in children and

between office and daytime ambulatory BP in adolescents (Stergiou et al. 2015).

Although this changing relationship between the three BP measurement methods might appear rather complex for clinical practice, it highlights the importance of using the respective normalcy tables for children and adolescents for accurate evaluation. Indeed, in an analysis of the differences in BP thresholds among the three BP measurement methods (assessed as the 50th and 95th percentiles by gender and age), percentiles of home BP were consistently lower than daytime ambulatory BP in both boys and girls (by 4–8 mmHg for systolic and diastolic BP for the 50th percentile). Moreover, home BP seemed to have similar ability as ambulatory BP to illustrate the change in systolic BP that occurs with increasing age. However, for diastolic BP, both methods reveal negligible changes with increasing age (Stergiou et al. 2011b). More specifically, the range of the home BP change with increasing age from 7 to 16 years was similar to ambulatory BP (for systolic BP, 15–21 mmHg in boys and 6–11 mmHg in girls and for diastolic BP, 1–4 mmHg in boys and girls). However, the range of office BP levels across the same age subgroups was considerably wider than that of out-of-office measurements (more evident for diastolic BP). A possible explanation might be that the effect of the office environment and the observer on measured office BP is not the same in all children and adolescents, resulting in the white-coat and masked hypertension phenomena. Another explanatory assertion might be that the automated (oscillometric) BP measurement technique used to define the normal range for home and ambulatory BP might be less sensitive than the auscultatory technique to reveal the diastolic BP changes with increasing age in children (Stergiou et al. 2011b). However, an important conclusion from these data is that in children and adolescents, home BP appears to be as reliable as ambulatory BP in quantifying the age-related BP rise.

### Reproducibility of Home BP

A small study in children and adolescents investigated the short-term reproducibility of office,

home, and ambulatory BP (Stergiou et al. 2005a). A 4-day home BP schedule with duplicate morning and evening measurements repeated after 2 months had superior reproducibility to office BP measurements and similar to that of ambulatory BP monitoring (standard deviation of differences 7.0/4.3 mmHg for systolic/diastolic home BP, 10.4/6.3 for office BP and 5.5/4.3 for 24-h, 5.9/5.0 for daytime, and 7.0/5.0 for nighttime ambulatory BP) (Stergiou et al. 2005a). The long-term reproducibility of home BP (12 readings obtained within 3 days and repeated after 17 months) was investigated in 48 children and adolescents and again was found to be superior to that of office BP (standard deviation of differences 8.3/6.5 mmHg for systolic/diastolic home versus 13.9/10.7 for office BP) (Stergiou et al. 2009b). Another study in 40 hypertensive children and adolescents showed a remarkable stability of systolic and diastolic mean BP values during the study period of 13 days of home BP monitoring (Furusawa et al. 2009). Indeed, the standard deviation of differences showed a significant decline only for diastolic BP values from the fifth home BP monitoring day, which difference tended to be eliminated by the end of the study (Furusawa et al. 2009). Taken together these data suggest that, as in the adults, home BP values are more reproducible than office measurements and as reproducible as ambulatory BP monitoring in children and adolescents.

### Diagnostic Value of Home BP

The basis for diagnosis and clinical management of children with hypertension has traditionally been conventional office BP measurements. However, out-of-office BP monitoring methods are valuable for the confirmation of normotension or hypertension and are now regarded as indispensable tools for the detection of the white-coat and masked hypertension phenomena (Flynn et al. 2014; Lurbe et al. 2016). Evidence is accumulating that, as in adults, home BP has similar diagnostic value as ambulatory BP monitoring in the detection of hypertension phenotypes in children and adolescents (Table 3).

In the ESCAPE study, home BP measurements were found to accurately diagnose hypertension (Table 3) when ambulatory BP monitoring was used as the reference method (Wühl et al. 2004). Furthermore, a study by Stergiou et al. (2008b) including 102 children and adolescents referred to a hypertension clinic showed that home and ambulatory BP monitoring might be interchangeable in the detection of white-coat or sustained hypertension, with clinically important disagreement between ambulatory and home BP in the diagnosis of hypertension observed in only 8% of the cases (Fig. 2). The results of this study on the diagnostic value of home BP monitoring for detecting white-coat, masked, and sustained hypertension compared to ambulatory BP

monitoring as the reference method are presented in Table 3 (Stergiou et al. 2008b). Similarly, another study in 81 children and adolescents referred for elevated office BP reported a moderate agreement between ambulatory and home BP in diagnosing hypertension in 85% of the participants (Stergiou et al. 2011a). Finally, Furusawa et al. (2011) studied 40 hypertensive patients (75% with secondary hypertension) and reported considerable diagnostic agreement for hypertension by ambulatory and home BP, suggesting that in hypertensive children and adolescents home and ambulatory BP monitoring are comparable methods.

An important observation is that sizable studies in healthy children and adolescents using either

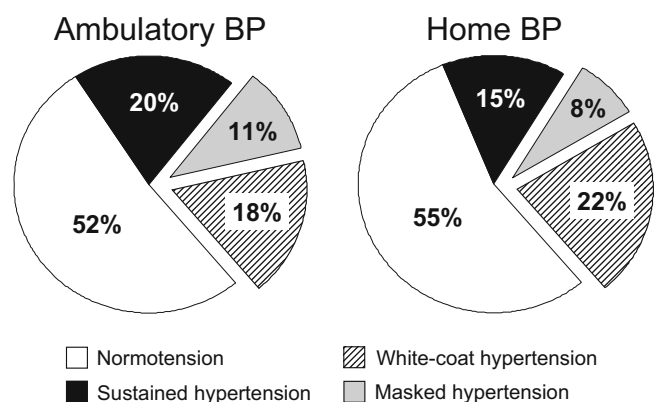
**Table 3** Diagnostic value of home blood pressure monitoring compared to ambulatory monitoring as the reference method

Study	N	Population	Diagnosis	Sen/Sp/PPV/ NPV (%)	Agreement (%)	Kappa
Wühl et al. (2004)	118	Children and adolescents with CRF	AH	52/82/47/85	75*	0.33*
			MH	38/92/25/95*	88*	0.24*
			WCH	74/91/71/92*	87*	0.64*
			SH	58/93/61/92*	87*	0.52*
Stergiou et al. (2008b)	102	Children and adolescents referred for elevated BP	AH	55/92/74/82	80	0.50
			MH	36/96/50/93	NR	0.36
			WCH	89/92/70/98	NR	0.73
Stergiou et al. (2011a)	81	Children and adolescents referred for elevated BP	AH	NR	85	0.53
Furusawa et al. (2011)	40	Hypertensive children and adolescents	SH	NR	NR	0.56

BP blood pressure, AH ambulatory hypertension, SH sustained hypertension, MH masked hypertension, WCH white-coat hypertension, Sen sensitivity, Sp specificity, PPV positive predictive value, NPV negative predictive value, NR not reported, CRF chronic renal failure

\*Values calculated by data provided in the published papers

**Fig. 2** Prevalence of white-coat, masked, and sustained hypertension diagnosed using home or awake ambulatory blood pressure monitoring among 102 children and adolescents referred to a hypertension clinic (with permission by Stergiou et al. 2008b). BP blood pressure



ambulatory or home BP monitoring reported the prevalence of masked hypertension to be higher than that of sustained hypertension and white-coat hypertension taken together. In the Arsakeion school study which included 765 children and adolescents, masked hypertension (detected by home monitoring) was twice as common as white-coat hypertension or sustained hypertension (Stergiou et al. 2009c). Similar findings were reported by Lurbe et al. (2005) using ambulatory BP in 592 healthy children and adolescents who attended a pediatric outpatient clinic for a preventive health checkup (Fig. 3).

Taken together these data suggest, that in children and adolescents, home BP is useful for the detection of white-coat and masked hypertension. However, at the present time because the available evidence for ambulatory BP monitoring in children is much stronger, this method should be preferred for diagnosis. Until more data for home BP become available in children (particularly on its relationship with target-organ damage), this method should be used for diagnosis only when ambulatory BP monitoring is not available or not tolerated.

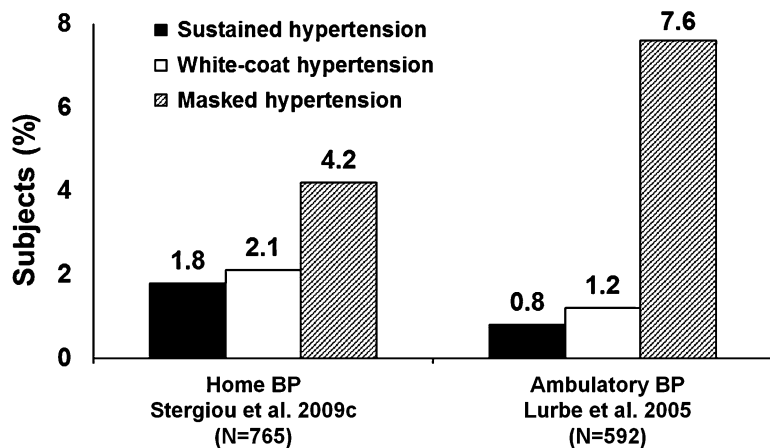
### Relationship with Preclinical Target-Organ Damage

Current guidelines for hypertension in adults are based on large, long-term observational and interventional outcome studies with hard endpoints of

morbidity and mortality (Lewington et al. 2002; Mancia et al. 2013). However, in children and adolescents such studies are not feasible as the cardiovascular events are far in the future requiring extremely long follow-up. During this time, multiple confounding factors will influence cardiovascular risk, thereby diluting the net effect of treatment-induced BP decline. Thus, large intervention studies in pediatric hypertension are lacking and unlikely to be available, and evidence about threshold BP values for intervention and BP goals is not expected to be available (Karpettas et al. 2013; Lurbe et al. 2016; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). As a result, several recommendations for hypertension management in children and adolescents are based on statistical considerations and assumptions or on extrapolation from evidence obtained in adults.

In hypertensive children and adolescents, the presence of preclinical (asymptomatic) target-organ damage is of paramount importance in the assessment of the cardiovascular risk and decision-making (Lurbe et al. 2016; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). Since no alternate well-studied endpoints related to hypertension are available for determining the prognostic value of BP for cardiovascular events, the main indices of target-organ damage in the pediatric population are echocardiographic left ventricular hypertrophy (mass and index),

**Fig. 3** Prevalence of sustained, white-coat, and masked hypertension diagnosed by home or ambulatory blood pressure monitoring among healthy children and adolescents. BP blood pressure



increased carotid intima-media thickness, microalbuminuria, proteinuria, and decreased glomerular filtration rate (Lurbe et al. 2016; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). Of these indices, left ventricular hypertrophy has been the most extensively studied marker of preclinical target-organ damage, based mainly on studies using ambulatory BP monitoring (Kollias et al. 2014). A recent systematic review identified scarce evidence on the association of home BP with target-organ damage. Of the evidence that is available, the majority assess left ventricular mass and less so arterial stiffness, with no evidence regarding carotid atherosclerosis or albuminuria (Kollias et al. 2014).

A study in 54 children and adolescents referred for suspected hypertension (24% with primary hypertension) showed both home and ambulatory systolic BP values to be closely associated with echocardiographic left ventricular mass (correlation coefficient  $r$  0.53 for home and 0.55 for ambulatory BP), whereas office BP tended to exhibit lower correlation coefficients (Stergiou et al. 2011a). Conversely, in a study involving children with renal transplantation, no association between maximum or minimum home BP and left ventricular mass index was found. However, home BP monitoring was not standardized in this study and performed under unreported conditions using various devices which may have influenced the results (Kitzmueller et al. 2004).

A single study investigated arterial stiffness in children assessed by pulse wave velocity measurements (Stergiou et al. 2011a) and reported similar association with home and ambulatory BP measurements ( $r$  0.52 and 0.50 for systolic ambulatory BP and home BP, respectively). Moreover, step-wise multivariate regression analysis showed systolic home BP to be the strongest predictor of pulse wave velocity.

## Home BP in Clinical Research

Home BP has been shown to be useful in clinical hypertension research in adults (Stergiou and Ntineri 2016), whereas in children and adolescents

adequate relevant evidence is limited. A small study reported data on the reproducibility of home BP and showed that this is superior to that of office BP measurements, which suggests that home BP monitoring can improve the statistical accuracy (power) of clinical trials in pediatric hypertension thereby allowing smaller samples to be studied (Stergiou et al. 2005a). Other advantages of home BP compared to classic office measurements, such as the lack of placebo effect and white-coat hypertension and masked phenomena, are also important for clinical research in pediatric hypertension. Furthermore, home BP monitoring has lower cost than ambulatory monitoring and is more appropriate for long-term trials which require repeated evaluation.

Several studies have suggested that home BP monitoring can be successfully implemented into large clinical trials assessing several different aspects of pediatric hypertension (Asayama et al. 2012; Stergiou et al. 2009c; Wühl et al. 2004). The Arsakeion school study performed home BP monitoring in 778 healthy children and adolescents and showed home BP to be more closely associated with obesity (body mass index) than office BP (Karatzi et al. 2009). The Tohoku Study of Child Development in Japan which included 382 pairs of mothers and their 7-year-old offspring showed that home BP might be superior to office BP in assessing heritability and intrafamilial aggregation of BP. Mother-offspring correlations were closer for home BP than office BP for systolic (correlation coefficient  $r$  0.28 versus 0.06) and diastolic BP (0.28 versus 0.02), with only the correlations for home BP being statistically significant (Asayama et al. 2012). The same study was able to identify subtle, yet important differences in the effect of breastfeeding in preventing BP elevation even in young children, which was demonstrated using home but not office BP (Hosaka et al. 2013). A single study that introduced home BP telemonitoring in children with hypertension showed this method to be feasible, well accepted, easy to use, and considered as helpful by participants (Bedra and Finkelstein 2015).

The available evidence on the potential of home BP monitoring in the evaluation of the

antihypertensive medication efficacy is scarce. An open-label, uncontrolled pilot study in 11 hypertensive children assessing the effects of the angiotensin receptor blocker candesartan showed significant BP decline in office and ambulatory BP, but not in home BP (Franks et al. 2008). In the ESCAPE trial, which investigated the effect of strict BP control with angiotensin-converting enzyme inhibitors on the progression of nephropathy, 118 children and adolescents with chronic renal failure performed 3–21 home BP measurements over 2–7 days, yet to date no data on the use of these measurements in assessing the BP-lowering effects of these medications have been reported (Wühl et al. 2004).

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## Clinical Application of Home BP Monitoring

### Feasibility of Home BP Monitoring

Home BP monitoring has been consistently shown to be feasible in the pediatric population, with the vast majority of children and adolescents being able to perform a several-day schedule and provide an acceptable number of valid BP measurements at home, with or without (in older children and adolescents) their parents' assistance. In the Arsakeion school study, 70% of the 778 healthy participants provided all the requested home readings (duplicate morning and evening measurements for 3 days) and 95% provided at least two thirds of the requested readings (Stergiou et al. 2007). A study in 105 children and adolescents referred to a hypertension clinic for elevated BP reported that only 3% of the participants performed <50% of the requested 24 home BP readings (Stergiou et al. 2008b). In a study of 43 children and adolescents with type 1 insulin-dependent diabetes mellitus who monitored home BP for 3 days, 61% of the participants provided all the requested measurements and 88% provided at least one third of the requested measurements (Gompels and Savage 1992). In the ESCAPE trial, which studied 118 patients with chronic renal failure aged 3–19 years, Wühl et al. (2004) reported that of requested three times daily BP

measurements, morning readings were obtained in 89% of the participants, evening readings in 83%, and midday readings in 61%. In addition, in a study by Salgado et al. (2011) only 3.4% of the participants did not obtain the number of readings necessary for analysis. In line with the abovementioned findings, Furusawa et al. (2009) reported an adherence of 91% among study participants in the requested home BP monitoring schedule including 78 measurements (6 measurements per day for 13 days). Interestingly, the high feasibility and applicability of home BP monitoring in children and adolescents did not seem to be influenced by the family income or education level (Salgado et al. 2011).

### Home BP Monitoring Schedule

Consideration of the optimal schedule for home BP monitoring is important for appropriate clinical application. In adults, a 7-day (but no less than 3-day) schedule with duplicate morning (before drug intake if treated) and evening home BP measurements taken in the sitting position after few minutes rest is recommended by both American and European guidelines (Parati et al. 2008; Pickering et al. 2008). The average of all readings should be evaluated after excluding those of the first day (Parati et al. 2008; Pickering et al. 2008). This home BP monitoring schedule has been tested in children and adolescents in 3 days (Stergiou et al. 2007) and 6–7 days (Furusawa et al. 2009; Stergiou et al. 2008a, b), and the findings were similar to those for adults (Furusawa et al. 2009; Stergiou et al. 2008a). Thus, the abovementioned schedule of home BP monitoring for 6–7 (minimum 3) routine school days appears to be appropriate for the assessment of average home BP in individual children in clinical practice (Table 4; Lurbe et al. 2016; Stergiou et al. 1998, 2008a; Stergiou and Parati 2007). This schedule should be performed for the initial diagnosis in children with suspected hypertension and also before each follow-up visit to the doctor in children with treated hypertension. Between office visits for the long-term follow-up of adequate BP control of children treated for



**Table 4** Instructions for home blood pressure monitoring in children and adolescents

<i>Devices</i>
Use automated electronic (oscillometric) upper-arm devices that have been successfully validated specifically in children
Ensure the appropriate cuff size for the individual's arm circumference is utilized
Select devices equipped with automated memory or PC link capacity when available
<i>Conditions</i>
Measurements may be taken by parents of young children, or self-measurements may be appropriate for some adolescents
Perform measurements in a quiet room after 5 min of rest in the seated position with back supported and arm resting at heart level
<i>Schedule</i>
Monitor home blood pressure for no less than 3 routine school days but preferably 6–7 days
Obtain duplicate morning and evening measurements (with 1 min intervals) on each day blood pressure is monitored
<i>Interpretation</i>
Calculate the average of all measurements after discarding the first day
Evaluate the average value using the available normalcy data for home blood pressure in children
Average home blood pressure $\geq$ 95th percentile for gender and height indicates home hypertension

hypertension, one to two home measurements per week, or even less frequent, might suffice (Parati et al. 2008).

### Normal Range of Home BP

Normalcy data for home BP in children and adolescents derived from the Arsakeion school cross-sectional study (Stergiou et al. 2007) in 778 children and adolescents in Greece have been published as percentile tables according to gender and height (Table 5). Home BP monitoring was performed using an electronic (oscillometric) device (Omron 705 IT) which has been validated for accuracy specifically in children and adolescents (Stergiou et al. 2006). In the original paper, home BP percentiles were provided by 10-cm height subgroups, and in a second analysis these were also provided by age (Stergiou et al. 2011b).

Like the norms for office BP, the 50th percentile reported in the table represents the BP level at the midpoint of the normal range (where the average child of this group is), and home BP values above the 95th percentile should be considered hypertensive. While tables for both home and ambulatory BP are based on a much smaller sample than similar normal tables for office BP (or ambulatory BP) (Stergiou et al. 2011b), out-of-office BP measurement methods are known to have superior reproducibility to office BP measurements thereby reducing the sample size required (Stergiou et al. 2005a, 2009b). Another limitation to both of these tables is that they lack geographic diversity and thus may not be applicable to all populations.

### Devices for Home BP Monitoring

The auscultatory method is still regarded as the gold standard for BP measurement in children and adolescents (Flynn et al. 2017; Lurbe et al. 2016; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). However, for both home and ambulatory BP monitoring, electronic (mostly oscillometric) devices are recommended (Flynn et al. 2014; Lurbe et al. 2016). This is because almost all the available evidence in children and adolescents on the clinical application of both home and ambulatory BP monitoring (Lurbe et al. 2016; Stergiou et al. 2009a) as well as their reference values (Stergiou et al. 2007) have been obtained using electronic devices. In addition, the complexities of the auscultatory technique in the pediatric population make it less amenable to home measurements. The need for recording the fourth Korotkoff sound in case of sounds audible until 0 mmHg for defining diastolic BP, the weak Korotkoff sounds, the small arm dimensions, the difficulty of the younger children to stay still during measurement, and the presence of a non-experienced observer make the auscultatory technique quite tricky and unreliable for home BP monitoring in children and adolescents. An additional advantage of the automated home BP monitors is that they avoid observer error and bias.

**Table 5** Normalcy tables for home blood pressure (mmHg) in children and adolescents by gender and height (with permission from Stergiou et al. (2007))

Height (cm)	N	Percentiles for boys ( <i>n</i> = 347)		N	Percentiles for girls ( <i>n</i> = 420)	
		50th	95th		50th	95th
120–129	23	105/64	119/76	36	101/64	119/74
130–139	51	108/64	121/77	51	103/64	120/76
140–149	39	110/65	125/77	61	105/65	122/77
150–159	41	112/65	126/78	71	108/66	123/77
160–169	45	115/65	128/78	148	110/66	124/78
170–179	91	117/66	132/78	46	112/66	125/79
180–189	57	121/67	134/79	7	114/67	128/80

Reporting bias by users can be avoided as well when automated memory, PC link, or tele-monitoring are used, which ensure that a reliable and unbiased evaluation of home BP can be obtained (Myers and Stergiou 2014). Thus, electronic BP monitors are indispensable for both ambulatory and home BP monitoring in children and adolescents.

Oscillometric devices measure BP by detecting the pressure oscillations created in the arm during cuff deflation (inflation in a few devices). An oscillometric curve is created, and mean BP is determined directly from this curve at the point of maximal oscillation. Systolic and diastolic BP values are not directly measured, but calculated using a manufacturer- and device-specific mathematical algorithm. Because these algorithms were originally developed for adults who have stiffer arteries and different (longer and/or larger) oscillations, some oscillometric devices might not be accurate in children (Karpettas et al. 2010).

The accuracy of the device is fundamental to any method of BP measurement (American National Standards Institute, Association for the Advancement of Medical Instrumentation and International Organization for Standardization 2013; O'Brien et al. 1993, 2010). Thus, the accuracy of all BP monitors should be tested in independent studies using an established validation protocol (American National Standards Institute, Association for the Advancement of Medical Instrumentation and International Organization for Standardization 2013; O'Brien et al. 1993, 2010). Validation studies of BP monitors in children face several challenges due to the special structural and functional characteristics of

children including a wide variation of arm sizes requiring different cuff sizes, very low BP levels, faint Korotkoff sounds, and difficulty in detecting diastolic BP. Thus, the validation protocols developed for adults are not fully applicable in children and several adaptations are needed. Additionally, there are data suggesting that an electronic BP monitor that has been successfully validated in adults might not be accurate in children (Chioloro et al. 2014). Thus, it is recognized that children should be regarded as a special group requiring separate validation studies for automated BP monitors (American National Standards Institute, Association for the Advancement of Medical Instrumentation and International Organization for Standardization 2013; O'Brien et al. 1993, 2010).

Despite the widespread use of automatic BP monitors in pediatric practice and their endorsement by hypertension societies (Lurbe et al. 2016), very few successful validation studies of such BP monitors in children and adolescents have been published (Furusawa et al. 2005; Narogan et al. 2009; Stergiou et al. 2006). Similarly, very few ambulatory BP monitors have been independently validated in the pediatric population. However, it is scientifically problematic that the normalcy tables recommended in Europe (Lurbe et al. 2016) and the USA (Flynn et al. 2014) for the evaluation of ambulatory BP in children are based on a single study that used a BP monitor which satisfied validation criteria in children only for systolic BP children (Belsha et al. 1996).

The largest pediatric validation study of a home BP monitor included 197 children and

adolescents (age 6–16 years) and showed the Omron 705 IT home monitor to meet both European and American validation criteria (Stergiou et al. 2006). Validation data were provided for quartiles of age, body size, and BP levels (Stergiou et al. 2006), and all were within the US Association for the Advancement of Medical Instrumentation (AAMI) protocol requirement of mean BP difference within 5 mmHg with standard deviation within 8 mmHg (Association for the Advancement of Medical Instrumentation 1993). It is important that this validated device was the monitor used to create the only currently available normalcy tables for home BP in children and adolescents (Stergiou et al. 2007). The A&D UA-778 home monitor was also validated in a study in 85 children aged 4–15 years which reported that the device was accurate using both the British Hypertension Society (BHS) and the AAMI protocol criteria (Association for the Advancement of Medical Instrumentation 1993; Narogan et al. 2009; O'Brien et al. 1993). On the other hand, the OMRON M1 home monitor was evaluated in 47 children and did not pass the BHS protocol criteria (Barker et al. 2000). The Omron 705-CP home monitor was also successfully tested in a validation study, but only in adolescents (Furusawa et al. 2005), who according to the American National Standards Institute/ Association for the Advancement of Medical Instrumentation/ International Organization for Standardization (ANSI/AAMI/ISO) validation protocol are not regarded as a special population for validations and are investigated together with adults in general population validation studies. Last, a validation study using BHS and AAMI protocols to evaluate two electronic devices (Labtron and Marshall 85) in 106 children and adolescents concluded that both were inaccurate (Wells et al. 1998).

Unfortunately, the accessibility of the home BP monitors that have been successfully validated in children may be limited as regulatory bodies vary between countries and marketing strategies of companies lead to frequent “upgrades” and phasing out of previous models over time. Additionally, the wide spread clinical application of home monitoring in children is further limited by the

lack of availability of several cuff sizes for the majority of electronic home monitors. Recently multiple electronic wrist devices for home BP monitoring have become available. These are less accurate than the upper arm devices and are not recommended in adults (Parati et al. 2002, 2008; Pickering et al. 2008). There are currently no formal validation studies to support their use in children either, and a pilot study in pediatric patients with a wrist diameter greater 13.5 cm showed a large discrepancy of such devices from mercury sphygmomanometer (Navor-Galeana and Gutierrez-Martinez 2014).

### **Clinical Indications of Home BP Monitoring**

Home BP monitoring is useful in the initial evaluation of children with elevated BP, in order to detect white-coat and masked hypertension. However, as the current evidence for ambulatory BP monitoring in children is much stronger, this method should have the primary role in diagnosis with home BP monitoring being used if ambulatory monitoring is not available or not tolerated. Home BP monitoring is particularly useful and superior to ambulatory monitoring for repeated use and long-term follow-up. Thus, it can be used in the follow-up of children with prehypertension or white-coat hypertension as complementary to office and ambulatory monitoring and also in the long-term follow-up of children treated for hypertension, particularly in high-risk patients where strict BP control is crucial (nephropathy, diabetes type 1) (Lurbe et al. 2016).

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### **Conclusions**

Home BP monitoring is currently applied in clinical practice for the evaluation of BP in children and adolescents, and evidence from clinical trials is accumulating on its clinical relevance and application. Home BP monitoring is superior to conventional office measurements due to several advantages, including the detection of white-coat

and masked hypertension, lack of placebo effect, observer error, and bias, and higher reproducibility. Several trials in children and adolescents comparing home with office and ambulatory BP in terms of their absolute values and diagnostic ability have been published, as well as data on the optimal home BP monitoring schedule, and normalcy tables with thresholds (percentiles) for home hypertension diagnosis. However, the evidence for its relationship with preclinical target-organ damage and studies validating electronic home monitors in children are limited. Home BP monitoring appears to have high potential for wide clinical application in children and adolescents.

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## Cross-References

- ▶ [Ambulatory Blood Pressure Monitoring Methodology and Norms in Children](#)
- ▶ [Cohort Studies, Meta-analyses, and Clinical Trials in Childhood Hypertension](#)
- ▶ [Development of Blood Pressure Norms and Definition of Hypertension in Children](#)
- ▶ [Methodology of Casual Blood Pressure Measurement](#)
- ▶ [The Role of ABPM in Evaluation of Hypertensive Target-Organ Damage](#)

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## Abstract

The prevalence of hypertension in the pediatric population has increased substantially over the last 30 years. While the concomitant obesity epidemic has played a major role in the rise of pediatric hypertension, it is now clear that multiple factors influence the development of hypertension in children and adolescents. This chapter describes the prevalence of hypertension and risk factors associated with its development. Further, it examines the immediate- and long-term effects of early hypertension along with population-based strategies which may be helpful for reversing noted trends in hypertension.

## Keywords

African Americans • Asians • Bogalusa Heart Study • BP measurement technique • BP tracking • Cardiovascular risk factors • Carotid intima-media thickness • Caucasians • Epigenetics • Essential hypertension • Fructose • Heritability • Hispanic youth • Hispanics • Obesity

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## Introduction

The prevalence of pediatric hypertension has increased substantially in the last 30 years. While initially attributed to a concomitant rise in obesity, it is now clear that multiple factors contribute to the development of hypertension in children and adolescents. This chapter will describe the prevalence of hypertension and risk factors associated with its development. Further, it will examine the long-term effects of early hypertension and population-based strategies which may be useful in reversing noted trends in hypertension.

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## Prevalence of Pediatric Hypertension

Originally considered quite rare, hypertension has been increasingly recognized in pediatric populations over the last several decades. Changes in the prevalence of pediatric hypertension have been difficult to track owing to differences in measurement techniques, populations studied, definitions for hypertension, and reference values utilized. Current estimates suggest that up to 5% of children and adolescents have sustained hypertension across multiple measurement sessions as defined by the 2004 Working Group on Hypertension in Children (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents Task Force 2004). Hansen et al. (2007) noted in a retrospective review of over 14,000 healthy children seen for routine health maintenance that 3.6% of the population had sustained hypertension across three measurement sessions, while another 3.4% had sustained prehypertension. In a similar study of over 230,000 youth aged 6–17 years receiving health care through a large healthcare plan, 2.1% of the population had sustained hypertension (Koebnick et al. 2013). Another 4.8% had a BP in the hypertensive range on two occasions suggesting that with further follow-up, the prevalence of sustained hypertension may actually be higher. Additionally, over 30% of the population had an elevated BP (>90th percentile) during at least one healthcare encounter.

Given the high prevalence of white coat hypertension in the pediatric population, one might anticipate that rates of hypertension and prehypertension measured outside of the normal healthcare setting would be lower. In fact, a cross-sectional evaluation of 6790 junior and senior high school students in Houston, TX, participating in a school-based BP screening program, found that 15.7% of the population had an elevated BP (either prehypertensive or hypertensive) on at least one occasion (McNiece 2007b) as compared to the 30% reported by Koebnick et al. (2013). However, the prevalence of persistent hypertension was 3.2% – similar to rates seen in office-based surveys.

A large body of literature examining the prevalence of high BP at one measurement session exists. Because BP has been shown to normalize with repeated measurement sessions particularly in children who may have more BP variability and anxiety related to medical procedures, these studies are not completely accurate reflections of the prevalence of hypertension. However, because the rates of an elevated BP at one measurement session are much more frequently reported given their ease of measurement, these studies are useful in following trends in abnormal BP thus providing some insight into the changing landscape of pediatric hypertension.

A recent meta-analysis including 55 such studies and encompassing over 122,000 youth reported a pooled prevalence of high blood pressure at 11.2% (de Moraes et al. 2014). This rate was higher in boys (13%) versus girls (9.6%). Higher prevalence rates were also noted from countries with low to middle incomes and among those in which automatic oscillometric methods were used to measure BP. Thus, it is critical to consider the population sample as well as the BP measurement technique used when comparing studies reporting the prevalence of pediatric hypertension. Interestingly, despite the wide-held belief that the prevalence of hypertension is increasing in relation to the obesity epidemic, the de Moraes et al. meta-analysis (de Moraes et al. 2014) actually showed a decrease in high BP from 1988 to 2009 among boys and a trend (although not statistically significant) toward a decrease in high BP among girls in the face of rising rates of obesity among youth during this time frame (Ogden et al. 2016).

Another important observation regarding the increase in the prevalence of pediatric hypertension over the last few decades is a trend toward increasing primary ('essential') hypertension. Although secondary hypertension remains more common in children compared to adults, primary hypertension has become a more common diagnosis especially among adolescents where primary hypertension is seen in up to 85% of the population (Robinson et al. 2004; Silverstein et al. 2006; Yoon et al. 2014). Similarly, many traditional cardiovascular risk factors have now

been associated with the development of early hypertension.

more likely to develop persistent hypertension and thus warrant targeted interventions.

## Risk Factors for Pediatric Hypertension Obesity

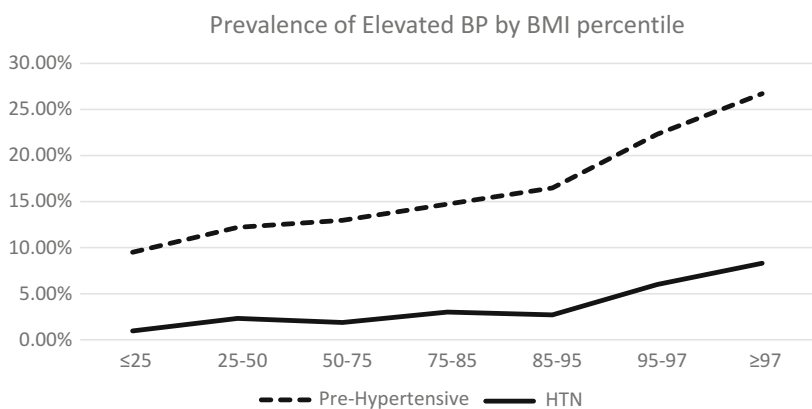
### Prehypertension

In 2004, the National High Blood Pressure Education Program Working Group recommended classifying children with BP between the 90th percentile for age, gender, and height (or 120/80 mmHg) and the 95th percentile as prehypertensive in order to identify children most likely to benefit from lifestyle interventions to prevent the development of sustained hypertension. Falkner et al. (2008) later demonstrated a progression of 7% per year from prehypertension to hypertension among adolescents in whom single BP measurements were obtained every 2 years as part of the National Childhood Blood Pressure survey. Redwine et al. (2012) attempted to further define the risk associated with prehypertension during adolescence by examining the progression to confirmed hypertension (across three measurement sessions) among 1006 students participating in a school-based BP screening program. Overall, the rate of development of persistent hypertension was 0.5% per year. This rate was significantly higher among students with prehypertension – up to 6.6% per year for those with BP > 90th percentile on all three occasions during baseline screening. Together, this evidence supports the concept that children with prehypertension are

The association between obesity and hypertension in the pediatric population has been well demonstrated across multiple settings and age groups (Herouvi et al. 2013). The prevalence of both prehypertension and hypertension increases dramatically once BMI exceeds the 85th percentile (Fig. 1). Additionally, obese adolescents (BMI > 95th percentile) have a ninefold increased risk for developing hypertension during adolescence as compared to their healthy-weight counterparts (Redwine et al. 2012). The mechanisms by which obesity contributes to hypertension are complex and still not completely elucidated. Increased sympathetic nervous activity, impaired sodium homeostasis, hemodynamic changes, renal dysfunction, endocrine abnormalities, oxidative stress, inflammation, and vascular injury are all likely contributors to the development of obesity-related hypertension, but the interactions between these various components remain uncertain (Susic and Varagic 2017).

Obesity is estimated to affect approximately 17% of the pediatric population in the USA, leaving 12.7 million children at risk for hypertension. The prevalence of obesity increases with age such that 20.5% of adolescents are obese compared to 8.9% of 2–5-year-olds (Ogden et al. 2015). Unfortunately, despite efforts to combat obesity over the

**Fig. 1** Prevalence of elevated BP by BMI among adolescents (Adapted from McNiece et al. 2007b)



last two decades, obesity rates have continued to rise among adolescents. There has been some improvement noted in obesity rates among younger children in the last few years – with a leveling off among school-aged children and a small decline seen in children <5 years (Ogden et al. 2016). One hopes that this trend will extend to improvement among adolescent obesity rates, as well, as these children progress through childhood and adolescence.

## Gender

Boys and men have a higher blood pressure than their female counterparts throughout most of their lifespan (Sandberg and Ji 2012). This phenomenon is preserved across human cultures and extends to other animal species as well. The gender difference in BP among humans develops at approximately 12–13 years of age. While younger children have similar BP levels, both SBP and DBP rise at a significantly faster rate in boys than girls beginning early in the second decade of life (Roberts and Maurer 1977). Evidence from animal and human studies suggests that females have lower activity of the renin-angiotensin-aldosterone system as well as reduced salt sensitivity. While this has been contributed, at least in part, to the protective effects of estradiol, the direct effects of the chromosomal dose differences of the X chromosome along with contributions from follicle-stimulating hormone, luteinizing hormone, and testosterone are also likely involved in determining the BP differences observed between genders (Sandberg and Ji 2012). It has also been suggested that women, in general, are more likely to exhibit healthy lifestyle behaviors (e.g., healthy eating, less sedentary behavior) which may contribute to the gender differences noted in BP in humans (de Moraes et al. 2014). This observation, however, may not be true of all populations. Interestingly, despite evidence that men develop persistent hypertension sooner, women have an increased hypothalamic-pituitary-adrenal response to stress, placing them more at risk for white coat hypertension (Sandberg and Ji 2012).

## Race/Ethnicity

Racial and ethnic differences for a number of cardiovascular risk factors are well described in adults, with African Americans having a greater burden of hypertension, obesity, and diabetes (Jones et al. 2002). These racial differences are evident early in life, although more consistently demonstrated in boys rather than girls (Rosner et al. 2009; Hardy et al. 2017). Cross-sectional surveys report that higher rates of hypertension are often present in both African American and Hispanic youth (Rosner et al. 2009; McNiece 2007). Additionally, African Americans are more likely to transition from normotensive to prehypertensive at a younger age (Hardy et al. 2017) and to have left ventricular hypertrophy or other cardiovascular risk factors at presentation (Brady et al. 2010).

While the racial/ethnic predisposition to hypertension is surely related to underlying genetic factors, socioeconomic factors also likely contribute to these disparities, as many minorities come from lower socioeconomic backgrounds in which obesity rates are higher and dietary intake is typically less ideal. These complex interactions are well-illustrated in a recent study by Cheung et al. (2017) that evaluated the interactions between race/ethnicity and obesity and the impact of those interactions on the presence of hypertension among over 21,000 adolescents participating in a school-based BP screening program. Within the entire population, hypertension was more prevalent among African Americans and Hispanics; however, among obese adolescents, hypertension was more common among Hispanics and Caucasians. In fact, the influence of obesity on the prevalence of hypertension clearly differed by race/ethnicity. Obesity had a much larger impact on the prevalence of hypertension among Hispanics [RR 5.81 for obese vs. normal-weight adolescents] as compared to Caucasians [RR 4.11], Asians [RR 3.30], and African Americans [RR 2.29].

## Socioeconomic Status

Like many other indicators of poor health, the early development of hypertension and cardiovascular

disease has been linked to lower socioeconomic status (National Center for Health Statistics 2011). Commonly defined by parental education levels, income, or occupation, low SES status in childhood increases the risk for hypertension both during childhood and later in adulthood. Living with both parents during the first 12 years of life was associated with a 46% decreased risk for adult hypertension among African American men participating in the University Family Study (Barrington et al. 2014). Additionally, prematurity and low birth weight, both of which are prevalent among lower socioeconomic populations, are correlated with the development of early hypertension (Bagby 2007). Finally, in a cross-sectional survey of 4951 Polish adolescents, maternal education level, paternal occupation, and income adequacy were all associated with high blood pressure (Kaczmarek et al. 2015). Adolescents whose mothers had a high level of education were 1.8 times less likely to have systolic hypertension and 2.8 times less likely to suffer from diastolic hypertension. Likewise, paternal unemployment [OR 1.53; CI 1.04, 2.25] and income inadequacy [OR 1.40; CI 1.17, 1.94] were associated with a greater risk for elevated systolic BP. Limited access to high-quality food (Domingos et al. 2016; Suarez et al. 2015), decreased physical activity (Dwyer-Lindgren et al. 2017), increased prevalence of obesity (Dwyer-Lindgren et al. 2017; Giskes et al. 2008), decreased access to medical care (McClurkin et al. 2015), increased levels of psychological stress (Dwyer-Lindgren et al. 2017), and increased smoking rates (Dwyer-Lindgren et al. 2017) have all been postulated to contribute to the association between low socioeconomic status and hypertension. On a positive note, transitioning from a lower to a higher socioeconomic class by adulthood is associated with improvement of elevated blood pressure noted early in life (Kelly et al. 2015).

### Genetic Determinants of Hypertension

An early family history of hypertension and/or cardiovascular disease has been frequently associated with hypertension among children and

adolescents (Niiranen et al. 2017). This observation has led many to search for the underlying genetic factors that explain this heritability. Early twin and familial studies suggest that BP is moderately inheritable (30–50%) (Miall and Oldham 1963). However, specific monogenetic mutations with a large phenotypic effect that result in familial hypertensive syndromes account for only a small amount of hypertension. These genetic defects are inherited along classical Mendelian inheritance pathways and are discussed in more detail elsewhere in this text.

Understanding the genetics underlying the development of primary hypertension has proven more challenging. To date, through exome sequencing and genome-wide association studies (GWAS), 43 genetic variants associated with hypertension have been identified that have been replicated in independent samples (Dodoo and Benjamin 2017). Unfortunately, the majority of these are only associated with an average 1 mmHg increase in SBP and 0.5 mmHg increase in DBP. Furthermore, in one analysis including 29 of these single nucleotide polymorphisms (SNPs), collectively these SNPs accounted for only 1–2% of the variance in BP noted (Ehret et al. 2011). Thus, there is a large proportion of the heritability of hypertension that remains to be explained. It has been suggested that up to 116 SNPs with a similar effect size as those previously identified may exist (Ehret et al. 2011). Additionally, the mechanism by which each of these SNPs contributes to the development of hypertension must be elucidated as many of these SNPs are located near genes not previously thought to contribute to blood pressure regulation (Ehret and Caulfield 2013). Finally, the impact of environmental and behavioral factors on the expression of these genes remains to be explored. Although still in its infancy, the field of epigenetics which explores the factors that alter gene expression and their association with disease likely holds the keys to truly understand the complex interactions between genetic and environmental factors that underlie the development of primary hypertension.

## Dietary Factors

The impact of sodium intake on blood pressure elevation is well known. The average intake of sodium among children and adolescents in the USA is currently estimated to be 3387 mg per day – an amount that far exceeds current recommendations for the maximum daily intake of healthy adults (Yang et al. 2012). The majority of this sodium intake (>75%) is derived from processed and fast foods (Mattes and Donnelly 1991). Higher levels of sodium intake have been associated with progressively higher systolic blood pressure levels as well as an increased risk for prehypertension among children and adolescents (Yang et al. 2012). Similarly, relatively small reductions in sodium lead to an almost immediate fall in BP, which although modest (1.17 mmHg and 1.29 mmHg for systolic and diastolic BP, respectively) if sustained over a lifetime would lead to a substantial reduction in overall cardiovascular morbidity and mortality (He and MacGregor 2006).

Salt sensitivity which is demonstrated by a rise in blood pressure following an increase in salt intake increases with age. Additionally, other risk factors including African American race (Falkner and Kushner 1990), obesity (He and MacGregor 2006), hyperinsulinemia (Falkner et al. 1992), and low birth weight (Simonetti et al. 2008) have been associated with increased salt sensitivity in youth. There is also a genetic component to salt sensitivity which remains to be explored although SNPs associated with salt sensitivity have been identified. Salt sensitivity has been linked to a greater risk for cardiovascular events in adults (Morimoto et al. 1997), and adolescents who exhibit salt sensitivity are more likely to develop hypertension as adults (Mu et al. 2012).

Other potential dietary contributors to hypertension include potassium deficiency and high fructose intake. Both population and clinical studies in adults demonstrate that higher potassium diets are associated with lower blood pressure, and low-potassium diets are associated with higher blood pressure (Falkner 2017). While studies in children and adolescents are less

consistent, there is some evidence to support the beneficial effects of potassium in the pediatric population as well (Simons-Morton and Obarzanek 1997). Finally, increased fructose intake has been proposed as a contributing factor to the recent rise in hypertension, metabolic syndrome, and type 2 diabetes (Johnson et al. 2007). In addition to promoting weight gain and obesity, fructose (through its metabolites) increases uric acid which may play a causative role in the development of primary hypertension by inducing vascular injury particularly within the kidney.

## Physical Activity

Increased physical activity has a clear impact on weight gain and obesity, but may also provide some protective effects with respect to hypertension by improving sodium balance and quality of sleep, thus indirectly influencing various metabolic mechanisms involved in the development and maintenance of elevated blood pressure, such as the development of insulin resistance, reduction in sympathetic tone, changes in sodium homeostasis, downregulation of the renin-angiotensin system, and reduction in arterial stiffness and endothelial dysfunction (Strambi et al. 2016). Despite strong evidence regarding the benefits of physical activity for adults, a recent review examining the health benefits of physical activity during childhood brings to light the dearth of knowledge regarding the relationship between physical activity and blood pressure in the pediatric population (Janssen and LeBlanc 2010). The three observational studies in children examining the relationship between physical activity and blood pressure levels suggest only a weak effect of increased physical activity levels on blood pressure. Interventional studies, however, have been more positive with significantly decreased levels of both systolic and diastolic blood pressure described following the introduction of an exercise training program. These effects were more pronounced for aerobic exercise (1.39 mmHg for systolic BP) than resistance training (0.61 mmHg).

## Significance of Hypertension in Childhood

There is currently no direct evidence linking hypertension during childhood to adverse cardiovascular events later in life. However, there is substantial evidence that blood pressure levels in childhood predict BP later in life and that early markers of hypertensive organ injury are present among hypertensive youth.

### BP Tracking

BP levels track from childhood to adulthood (Chen and Wang 2008) such that children with BP in the upper range of normal tend to have elevated BP as adults as well. This was well demonstrated by the Bogalusa Heart Study, which reported statistically significant correlation coefficients between childhood systolic and diastolic blood pressure levels and later adult blood pressure levels among 1505 children. Additionally, among young adult participants who developed hypertension, systolic and diastolic blood pressure was elevated during childhood among 48% and 41% of the population, respectively (Bao et al. 1995). Furthermore, a meta-analysis of 50 cohort studies confirmed the strong evidence that blood pressure tracks from childhood to adulthood with an average correlation coefficient of 0.38 for systolic blood pressure and 0.28 for diastolic blood pressure. The strength of blood pressure tracking increases with baseline age and decreases with follow-up length but does not vary across different race/population groups (Chen and Wang 2008).

Recently, investigators from the Childhood Determinants of Adult Health Study attempted to identify modifiable factors that would alter blood pressure tracking into adulthood (Kelly et al. 2015). They noted that among 798 participants, children with an elevated blood pressure had a 35% increased risk for having elevated blood pressure as adults. Decreased BMI, increased vegetable consumption, decreased alcohol intake, and an upwardly mobile SES status were all associated with an increased rate of normalization of blood pressure in adulthood.

## Target Organ Damage

It is now well recognized that the precursors of cardiovascular disease begin in youth; indeed, multiple preclinical cardiac and vascular changes are noted in children with hypertension and with other risk factors for cardiovascular disease. Left ventricular hypertrophy (LVH) is the most commonly reported type of target organ damage among hypertensive youth and is present in up to 40% of children at diagnosis, depending upon the population studied and the definition used to define LVH (Brady et al. 2008; McNiece et al. 2007a; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). Adults with LVH have a higher rate of cardiovascular morbidity and mortality (de Simone et al. 1995). And while multiple factors including both hypertension and obesity are associated with the development of LVH in children, elevated blood pressure appears to have an independent effect on its development given the observed dose-response between increasing left ventricular mass and blood pressure severity (McNiece et al. 2007a; Pieruzzi et al. 2015). LVH is also seen in children with prehypertension suggesting that target organ damage may occur at blood pressure levels below our current thresholds for therapeutic interventions (Urbina et al. 2011). Subtle alterations in cardiac function, manifest primarily as diastolic dysfunction, have recently been identified in hypertensive children as well (Agu et al. 2014).

Both structural and functional vascular changes have also been recognized in hypertensive youth. Autopsy studies performed as part of the Pathobiological Determinants of Atherosclerosis in Youth Study demonstrated that early atherosclerotic changes can be found in asymptomatic youth and young adults – the severity of which was associated with cholesterol level, blood pressure, and smoking behavior (McGill et al. 1995). Increased carotid intima-media thickness (an independent marker of stroke risk in adults) has been reported in several hypertensive populations (Lande et al. 2006; Sorof et al. 2003; Stabouli et al. 2005), and various markers of decreased vascular compliance including diminished pulse

wave velocity, amplified augmentation index, and increased carotid artery stiffness have been described as well (Urbina 2016). Microvascular changes are also apparent in the eye as children with higher levels of blood pressure have been shown to have significantly narrower retinal arterioles (Gopinath et al. 2010; Murgan et al. 2013). Finally, children and adolescents with hypertension also have subtle changes in neurocognition affecting their executive functioning (Lande et al. 2017). Together this data suggests that childhood hypertension does not simply pose a risk for adulthood hypertension. It is a sign of otherwise asymptomatic vascular injury that represents the beginning of the continuum of disease which progresses to overt cardiovascular disease later in life.

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### Population-Based Strategies to Reduce Hypertension

Hypertension has reached epidemic proportions among adults. Worldwide, hypertension is the leading risk factor for disease burden (Lin et al. 2010) and the leading cause of death (Chockalingam et al. 2006). In 2010, there were over two million more deaths attributed to high blood pressure than just 20 years earlier (Lin et al. 2010). With the introduction of effective vaccination campaigns, improvements in public sanitation, and successful educational programs to improve personal and public hygiene, hypertension and cardiovascular disease have surpassed infectious disease as the world's number one public health concern.

Until recently, most of the efforts to combat this epidemic have been targeted at individuals with the goals of decreasing personal risk factors for the development of hypertension, identifying elevated blood pressure when it is present, and effectively lowering blood pressure through lifestyle changes and medication to prevent worsening of cardiovascular disease. However, given how widespread a health concern hypertension has become, global strategies for preventing hypertension that target communities are important.

Campaigns to reduce sodium chloride consumption are the best described community-based efforts to prevent the development of hypertension. Finland was one of the first countries to initiate a systematic approach to decrease sodium chloride intake in the population through mass media campaigns, cooperation with the food industry, and implementation of sodium labeling legislation. Over time, these different measures led to a significant reduction in sodium chloride intake for the Finnish population from an average of approximately 12 g/day in 1979 to less than 9 g/day in 2002 (He 2009). In 2003, the UK began similar efforts to reduce sodium intake within the country. As part of this effort, the Food Standards Agency began working with manufacturers to cut sodium in processed food by developing voluntary maximum sodium targets for specific food. This led to an estimated 9.5% decrease in population sodium intake within just 5 years (Smith-Spangler et al. 2010). Several other countries including Canada, Ireland, Australia, the Netherlands, France, and Sweden have followed suit with their own salt reduction campaigns after noting the success in the UK (He 2009). The US Food and Drug Administration has only recently issued a draft of similar guidelines for voluntary sodium reduction targets for the food industry (United States Food and Drug Administration 2016). However, a recent cost-effectiveness analysis suggests that implementation of these standards if as effective as in the UK would avert >500,000 strokes and >480,000 myocardial infarctions over the lifetime of adults aged 40–85 who are alive today and save \$32.1 billion in medical costs (Smith-Spangler et al. 2010).

Reversing the epidemic of hypertension, however, will likely require a multifaceted approach that not only targets sodium reduction but also targets other modifiable risk factors for hypertension such as obesity and physical inactivity. Additionally multiple interventions targeting the same goal such as educational campaigns, creating safe spaces and built communities conducive to exercise, assuring easy access to quality food choices, and creating public policies that promote healthy behaviors will be critical to ensuring the success of these programs.

## Summary

Hypertension is no longer a rare disease among children and adolescents, and primary hypertension has become more common than secondary hypertension in the pediatric population. Multiple risk factors influence the development of hypertension, and while hypertensive children will be more likely to become hypertensive adults, they also already exhibit target organ damage related to their elevated blood pressure. Both individual- and population-based strategies will be critical to reversing the worldwide epidemic of hypertension and cardiovascular disease.

## Cross-References

- ▶ [Endothelial Dysfunction and Vascular Remodeling in Hypertension](#)
- ▶ [Epidemiology of Cardiovascular Disease in Children](#)
- ▶ [Ethnic Differences in Childhood Blood Pressure](#)
- ▶ [Heritability and Familial Aggregation of Blood Pressure](#)
- ▶ [Hypertension in Children with Type 2 Diabetes or the Metabolic Syndrome](#)
- ▶ [Hypertension in Older Adolescents and Young Adults](#)
- ▶ [Monogenic and Polygenic Contributions to Hypertension](#)
- ▶ [Obesity Hypertension: Clinical Aspects](#)
- ▶ [Primary Hypertension in Children](#)
- ▶ [Stress and Salt Sensitivity in Childhood Hypertension](#)
- ▶ [The Role of Dietary Electrolytes and Childhood Blood Pressure Regulation](#)
- ▶ [Value of Routine Screening for Hypertension in Childhood](#)

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## Abstract

Atherosclerosis, the major cause of acquired cardiovascular disease, has its origins in childhood. The development of early atherosclerosis is directly related to the major cardiovascular risk factors: hypertension, dyslipidemia, tobacco use, diabetes, obesity, and physical inactivity. The presence of risk factors in childhood is associated with measures of subclinical atherosclerosis later in life, and risk factors assessed in children are highly likely to persist into adulthood. Thresholds for optimal levels of cardiovascular risk factors in childhood have been developed, and evidence-based strategies for the management of cardiovascular risk in childhood have been published.

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## Keywords

Hypertension • Cholesterol • Tobacco • Obesity • Risk factors • Children • Heart disease • Atherosclerosis

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## Introduction

Hypertension is one of several major risk factors for the future development of atherosclerosis and atherosclerosis-related morbidity. The additional major risk factors that precede myocardial infarction, congestive heart failure, stroke, peripheral arterial disease, and abdominal aortic aneurysm include dyslipidemia (elevated LDL cholesterol, elevated triglycerides), tobacco use, and diabetes mellitus (Anonymous 2011). Age, gender (female

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**Table 1** Risk factors for atherosclerosis

<b>Major modifiable risk factors</b>
Hypertension
Dyslipidemia (elevated LDL cholesterol, low HDL cholesterol, elevated triglycerides)
Tobacco use
Diabetes mellitus
<b>Not modifiable risk factors</b>
Age
Gender
Genetic history
<b>Factors that modify major risk factors and may be independent themselves</b>
Diet
Physical activity
Family history
Obesity
Low socioeconomic status

gender is protective), and genetic endowment are non-modifiable risk factors. Physical inactivity, obesity, family history, adverse nutrition, and low socioeconomic status are intimately related to the development of cardiovascular risk in adults and may function as independent risk factors as well (Table 1) (Anonymous 2011).

This chapter will review the relationship of the major risk factors to atherosclerosis in childhood and to the future development of atherosclerosis in adulthood. This relationship has led to two concepts of atherosclerosis prevention in youth: primordial prevention, that is, the prevention of the development of risk factors in the first place, and primary prevention, the identification of elevated risk and subsequent risk factor management. The epidemiology of risk factors in childhood and the development of risk as an adult will be discussed. An overview of the management of cardiovascular risk in childhood, particularly in the context of hypertension, will be provided.

## Atherosclerosis in Childhood

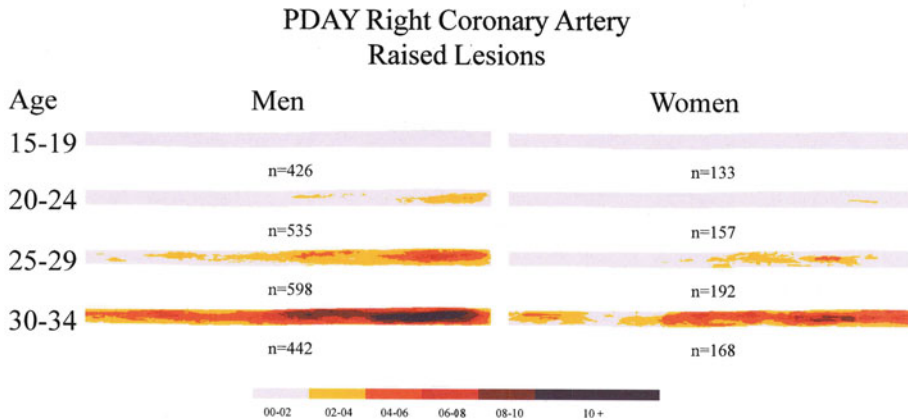
That the earliest lesion of atherosclerosis, the fatty streak, is present in children and more advanced lesions may present in young adulthood has been known since the 1950s (McGill et al. 2008). The

landmark Pathobiological Determinants of Atherosclerosis in Youth Study (PDAY) established the relationship of the major cardiovascular risk factors to early atherosclerosis by measuring atherosclerosis directly on postmortem examination in the coronary arteries and abdominal aorta of 15–34 year old men and women dying accidentally. Lesions were graded according to the standard American Heart Association classification ranging from Grade I (fatty streaks) to Grade V (obstructive plaques). These pathologic measurements were related to risk factors measured postmortem: height and weight, serum measures (lipids, thiocyanate, glycohemoglobin), renal artery thickness (a surrogate for blood pressure), and other physical measures such as panniculus thickness.

The major findings of the PDAY study were that atherosclerosis is present in adolescents and young adults, that the severity of atherosclerosis increases rapidly so that by early adulthood advanced lesions (American Heart Association Grade IV and V) are present, that the major cardiovascular risk factors are strongly related to atherosclerosis at all ages, and that the advancement of atherosclerosis to more advanced lesions is related not only to the major risk factors but the presence of multiple risk factors simultaneously (McGill et al. 2008). Atherosclerosis in women developed at a pace lagging about 5–10 years behind that in men (Fig. 1). Since most of the general population has at least one risk factor, the importance of public health measures and healthy behaviors in the prevention of atherosclerosis is a natural corollary of the PDAY findings. This is particularly true for children and adolescents when lesions are in the earliest and reversible phase (American Heart Association Grades I and II) (McMahan et al. 2006).

In PDAY, hypertension was evaluated categorically by renal artery thickness, a surrogate measure of hypertension associated with blood pressure greater than 140/90 mmHg in adults. The presence of hypertension was significantly associated with advanced atherosclerosis in both the coronary arteries and abdominal aorta (McGill et al. 1998).

Both non-HDL cholesterol and HDL cholesterol were related to atherosclerosis, both in the coronary arteries and the abdominal aorta. The



**Fig. 1** Increase in advanced atherosclerosis related to age and gender I shown in the heat maps

relationship with non-HDL cholesterol is continuous such that each 30 mg/dl rise in non-HDL cholesterol level is associated with the equivalent of 2–3 years of vascular aging. The relationship of HDL cholesterol to atherosclerosis was less strong but significant (McMahon et al. 2005).

Tobacco use produced its most severe impact in the abdominal aorta; however relationships to coronary atherosclerosis were also identified. More rapid advancement of lesions from fatty streaks to irreversible fibrous plaque was identified in smokers, particularly those with other risk factors (Zieske et al. 2005).

Diabetes mellitus was strongly associated with advanced atherosclerosis. It was the only risk factor to be associated with advanced lesions (American Heart Association Grades IV and V) in adolescents. Obesity (body mass index  $>30 \text{ kg/m}^2$ ) was related to atherosclerosis independent of other risk factors in men only (McGill et al. 1998, 2002).

To assess the importance of multiple risk factors on atherosclerosis development, the PDAY risk score was created. Each point in the risk score represents the rate of change in atherosclerosis associated with 1 year of aging. Thus, a risk score of 5 indicates the presence of atherosclerosis associated with being 5 years older than chronological age. Individuals with the highest scores had substantially more early lesions of atherosclerosis in late adolescence and substantially more advanced lesions by the first part of the fourth

decade of life (McMahon et al. 2005). These relationships are independent of cholesterol levels; thus the presence of a threshold level of non-HDL cholesterol is not necessary for the early development of atherosclerosis to occur (McGill et al. 2001).

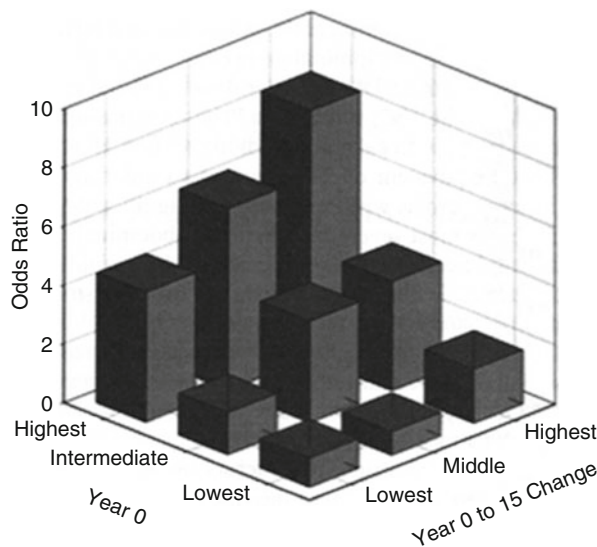
### Risk Factors in Childhood Predict Atherosclerosis in Adulthood

The concept of intervention in youth to prevent atherosclerosis in adulthood is supported by observations that for many risk factors, the presence of a given risk factor in youth is subsequently associated with premature cardiovascular morbidity and mortality in adulthood. For cholesterol, this evidence has been provided by genetic disorders such as familial hypercholesterolemia where in affected men; the median age of first cardiovascular event is late in the fifth decade of life and slightly older for women (Gidding et al. 2015a). Conversely defects associated with low cholesterol are protective against future disease (Cohen et al. 2006). Mendelian randomization studies suggest that for every mmol/L increase in LDL cholesterol, lifelong coronary heart disease risk is increased by 50% (Ference et al. 2012). Mendelian randomization studies also provide evidence for risk related to elevated triglycerides and lipoprotein (a) (Erqou et al. 2009; Nordestgaard 2016).

For tobacco, evidence is provided by the knowledge that tobacco is addicting, that tobacco use begins in adolescence, and that smoking cessation is associated with a dramatic reduction in future events (Anonymous 2012). For diabetes mellitus, evidence is provided by the natural history of type 1 diabetes mellitus with the primary cause of death in this condition being cardiovascular and also the absence of the gender protection against premature cardiovascular events. In contrast to other risk factors, female diabetics have cardiovascular events at the same age as men (De Ferranti et al. 2014). Type 2 diabetes mellitus is increasing in prevalence in adolescents and is associated with obesity, elevated triglycerides, low HDL cholesterol, and hypertension (Zeitler et al. 2012). In adolescents with type 2 diabetes mellitus, blood pressure and dyslipidemia worsen during the course of the disease (Anonymous 2013a, b).

Measures of subclinical atherosclerosis, including carotid intima media thickness (cIMT) and coronary calcium identified by CT scanning, are used in longitudinal epidemiologic studies and have provided additional evidence of the relationship of risk factors in youth to future atherosclerosis. In four separate longitudinal studies

conducted in various populations, the Muscatine Study, the Bogalusa Heart Study, the Cardiovascular Risk in Young Finns Study, and the Coronary Risk Development in Young Adults Study (CARDIA), risk factor measures obtained in adolescence or young adulthood predicted carotid IMT or calcium on CT scan better than risk factors measured at the time of the subclinical atherosclerosis measurement (Gidding et al. 2006b; Li et al. 2003; Mahoney et al. 1996; Raitakari et al. 2003). Resolution of risk from adolescence to adulthood is associated with no increase in carotid IMT compared to those with the absence of risk from childhood (Juonala et al. 2011). When the PDAY risk score was applied to the CARDIA and Young Finns cohorts, the PDAY risk score in adolescence or young adulthood best predicted future atherosclerosis, and change in risk score between initial measurement and the time of subclinical atherosclerosis assessment added predictive ability (Gidding et al. 2006b; McMahan et al. 2007). This prediction of future atherosclerosis holds for at least 25 years (Gidding et al. 2016). Improvement in risk during young adulthood prevented acquisition of subclinical atherosclerosis (Fig. 2).



**Fig. 2** The impact of baseline PDAY risk score and change in PDAY risk score over 15 years by tertile of risk is shown. The highest odds ratio is for those with

high baseline risk and high change in risk compared to those with low risk and no change in risk. A stair step relation is present

## The Rationale for Atherosclerosis Prevention by Primordial and Primary Strategies

Several lines of reasoning, including the information already presented in this chapter, have led to the understanding that the most effective prevention of atherosclerosis begins in youth (Robinson and Gidding 2014).

Cardiovascular risk factors identified in youth track into adulthood. A recent meta-analysis has confirmed that blood pressure in childhood has a tracking correlation of about 0.4 into adulthood with the development of obesity making development of hypertension in adulthood more likely (Chen and Wang 2008). Cholesterol levels have a similar tracking coefficient (Lauer and Clarke 1990). By its addictive nature, tobacco use in adolescence predicts adult tobacco use. Diabetes mellitus is an unremitting disease. Thus, the child at the upper end of the risk distribution is likely to remain in that position as an adult.

Equally important is the knowledge that atherosclerosis begins in youth and, prior to adulthood, is in its reversible phase. Individuals with no risk factors in the PDAY study have a low prevalence of atherosclerosis at age 30–34 years, and young adults with a low PDAY risk score have minimal subclinical atherosclerosis. Individuals who reach age 50 years and have no major cardiovascular risk have a lifetime risk of cardiovascular disease up to 95 years of age of 5% (Gidding et al. 2016; McMahan et al. 2006). Maintenance of a low cardiovascular risk state is highly protective against atherosclerosis-related morbidity as is improvement in obesity from childhood to early adulthood (Juonala et al. 2011).

Long-term adult longitudinal studies of cardiovascular disease demonstrate risk thresholds above which cardiovascular disease morbidity increases. These are LDL cholesterol levels above 100–110 mg/dl, blood pressure above 110–120/80 mmHg, presence of diabetes mellitus, and tobacco use (Anonymous 2001, 2003b). Animal models of atherosclerosis provide complimentary data where the introduction of risk above threshold levels produces disease (Steinberg and Gotto 1999). If one considers risk

distribution of generally healthy nonobese children, the vast majority, probably greater than 90%, have risk thresholds associated with no adult cardiovascular morbidity (Jolliffe and Janssen 2006; Messiah et al. 2008; Muntner et al. 2004). Thus, primordial prevention, or the prevention of risk factor development, is possible beginning in youth, if those behavioral factors associated with increase in risk are addressed.

Primary prevention strategies beginning in youth, or the high-risk approach, are considered because a small percentage of children are recognized to already have severe cardiovascular risk factors and premature atherosclerosis (Williams et al. 2002). For example, in heterozygous familial hypercholesterolemia, 28% of children have coronary calcium present on CT scans (Gidding et al. 1998a). Children with end-stage renal disease, type 1 diabetes mellitus, and chronic severe hypertension are known to have significantly premature cardiovascular morbidity and/or measurable cardiovascular end-organ injury in youth (Anonymous 2003a; Parekh and Gidding 2005). These children may benefit from aggressive risk factor reduction initiated at an early age. Though primary prevention clinical trials have not been performed in adolescents with high levels of risk, many presume that the benefit demonstrated in adult trials will also apply to this group.

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## Dyslipidemia

Universal lipid screening at age 9–11 years is now recommended for all US children either by a fasting lipid profile or non-fasting measurement of total cholesterol, HDL cholesterol, and non-HDL cholesterol. Fasting lipid measurement is also recommended over 2 years of age in children with obesity, hypertension, diabetes, positive family history of premature cardiovascular disease or elevated cholesterol, or other high-risk conditions (Anonymous 2011; Gidding et al. 2015a). Table 2 presents the classification of lipid levels for children from the 2011 NHLBI guideline. Triglycerides and HDL cholesterol have increased in importance because of the obesity epidemic. For non-HDL cholesterol, the difference between total

**Table 2** Lipid classification for children and adolescents (in mg/dl)

	Acceptable	Borderline	High
Total cholesterol	<170	170–199	≥200
Non-HDL cholesterol	<120	120–144	≥145
LDL cholesterol	<110	110–130	≥130
Triglycerides			
≤9 years	<75	75–100	≥100
>10 years	<90	90–130	≥130
	Acceptable	Borderline	Low
HDL cholesterol	≥45	40–44	<40

and HDL cholesterol is as useful as LDL cholesterol in the prediction of future cardiovascular risk and can be obtained in the non-fasting state (Anonymous 2011; McGill et al. 2008).

For US children, NHANES III provides a distribution of lipid levels. Fasting values are available for adolescents in that study (Jolliffe and Janssen 2006). There is significant variation in lipid levels by age with values increasing until about 2 years of age, then remaining relatively stable until prepuberty. Cholesterol levels rise at this time, fall significantly during rapid growth, and then slowly begin to climb in males and remain relatively stable in females throughout late adolescence (Labarthe et al. 1997). HDL cholesterol levels fall after puberty. Triglyceride levels increase during adolescence. There is a significant intrinsic variability of lipid measurements so that unless values are extreme, repeat measures are mandatory before classifying a child as abnormal (Gidding et al. 1998b).

Because of age-related changes and intrinsic variability in lipid levels, the prevalence of borderline dyslipidemia varies by age. In general, about 25% of children will have values for one lipid parameter considered borderline or higher. It is important to distinguish between extreme values (LDL cholesterol ≥160 mg/dl, non-HDL cholesterol ≥190 mg/dl, triglycerides ≥500 mg/dl) and borderline or mildly elevated levels as the latter do not require pharmacologic intervention and may improve spontaneously over time, particularly with successful behavioral intervention.

Genetic dyslipidemias are recognized by the presence of extreme values. Heterozygous familial

hypercholesterolemia has a prevalence of about 1:200 in the general population and is suggested by the presence of an LDL cholesterol level above 140–160 mg/dl with a positive family history for similar dyslipidemia in a parent or history of premature coronary artery disease (Gidding et al. 2015a). Homozygotes have total cholesterol levels in excess of 400–500 mg/dl, are at risk for coronary artery disease in the second and third decades of life, and require aggressive treatment to lower lipid levels at diagnosis, including lipid-lowering medications and plasmapheresis beginning at age 3–4 years. Hypothyroidism and nephrotic syndrome must be excluded in those with significant elevations of LDL cholesterol.

Fasting triglyceride levels above 150 mg/dl in a lean child or above 200–250 mg/dl in an obese child suggest an inherited disorder of triglyceride metabolism or familial combined hyperlipidemia. Homozygotes with severe disorders of triglyceride metabolism have levels >1000 mg/dl and require diets with <10% fat to prevent pancreatitis (Zappalla and Gidding 2009). Triglycerides can be transiently elevated to extreme levels with acute endothelial injury affecting lipase function; this can occur in diabetic ketoacidosis and in rare inflammatory disorders. Elevated triglycerides and other dyslipidemias may also be seen secondary to HIV, chemotherapy, and late after cancer chemotherapy. Triglyceride levels are highly variable so that unless a value is >500 mg/dl, a single value may not be used for classification of an abnormality.

The most prevalent dyslipidemia in the United States is the combination of elevated triglycerides and low HDL cholesterol. This is largely because of the obesity epidemic. In adults, the clustering of obesity, insulin resistance, hypertension, and dyslipidemia is called the metabolic syndrome (Anonymous 2001). No satisfactory childhood definition of this condition has been accepted; however, risk clustering is clearly present in overweight children and is likely associated with future cardiovascular morbidity (Anonymous 2011).

The initial treatment of dyslipidemia is dietary. Table 3 provides useful principles of diet management (Gidding et al. 2005; Gidding et al. 2009). For elevated LDL and non-HDL cholesterol, a



**Table 3** American Heart Association pediatric dietary strategies for individuals >2 years of age

Balance energy intake with energy expenditure to maintain normal growth
Engage in 60 min of moderate to vigorous physical activity daily
Emphasize deeply colored vegetables and fruits in the diet
Substitute vegetable fats low in saturated fat and <i>trans</i> fatty acids for most animal fats in the diet
Limit the intake of high sugar beverages
Choose whole grain over refined grain products
Use low-fat and non-fat dairy products on a regular basis
Consume fish, especially oily fish, at least twice a week
Reduce salt intake

diet low in saturated fat (< 7% of total calories, < 200 mg/day of cholesterol) should be implemented, in addition to the diet recommended in Table 3. Dietary fiber, particularly oat fiber, and plant sterols and stanols are also helpful in lowering LDL cholesterol. More information with regard to dietary treatment can be found in publications on the Internet from the American Heart Association, the USDA (Anonymous 2015; Wiegman et al. 2004), The National Cholesterol Education Program of the National Institutes of Health, Kids Health.org, and the American Academy of Pediatrics. For elevated triglycerides (below 750–1000 mg/dl), weight management is initial treatment. Avoidance of carbohydrates, particularly refined sugars, is critical. Avoidance of mono- and polyunsaturated fats is not necessary as they may be useful in maintaining or increasing associated low HDL cholesterol.

Pharmacologic treatment for elevated cholesterol is considered in children over 8–10 years of age with severely elevated LDL cholesterol and failed dietary management (Anonymous 2011; Wiegman et al. 2004, 2015). The algorithm in Fig. 3 presents the lipid pharmacologic treatment algorithm from the 2011 guideline on CVD risk reduction in youth (Anonymous 2011). Recommendations are stratified by the presence of cardiovascular risk factors. Statins are the initial management, and the goal of treatment is an LDL cholesterol < 130 mg/dl. Liver function should be monitored, and treatment is held for elevation of transaminases greater than three

times the normal. The presence of myalgia is an indication for withholding treatment as rhabdomyolysis can occur as a rare complication. Statins are not to be given during pregnancy or with breastfeeding. In children less than 10 years of age, statins can be considered in very high-risk settings. Randomized trials of statin treatment of up to 2 years duration have been reported (Mccrindle et al. 2007). One randomized trial has suggested that atherosclerosis progression as assessed by carotid IMT can be slowed by statin treatment, particularly if treatment is started in adolescence, but there are no trials of statin use in children demonstrating prevention of cardiovascular disease in adulthood (Rodenburg et al. 2007; Wiegman et al. 2004).

In the setting of multiple risk factors, statins may be initiated at lower LDL levels. In diabetics or those with two additional significant risk factors, statins should be considered for LDL level of 160 mg/dl (or 130 mg/dl if risk is considered significantly elevated) (Anonymous 2003a). Thus, in a patient with hypertension and an additional risk factor, statins would be initiated at this lower threshold (Anonymous 2011).

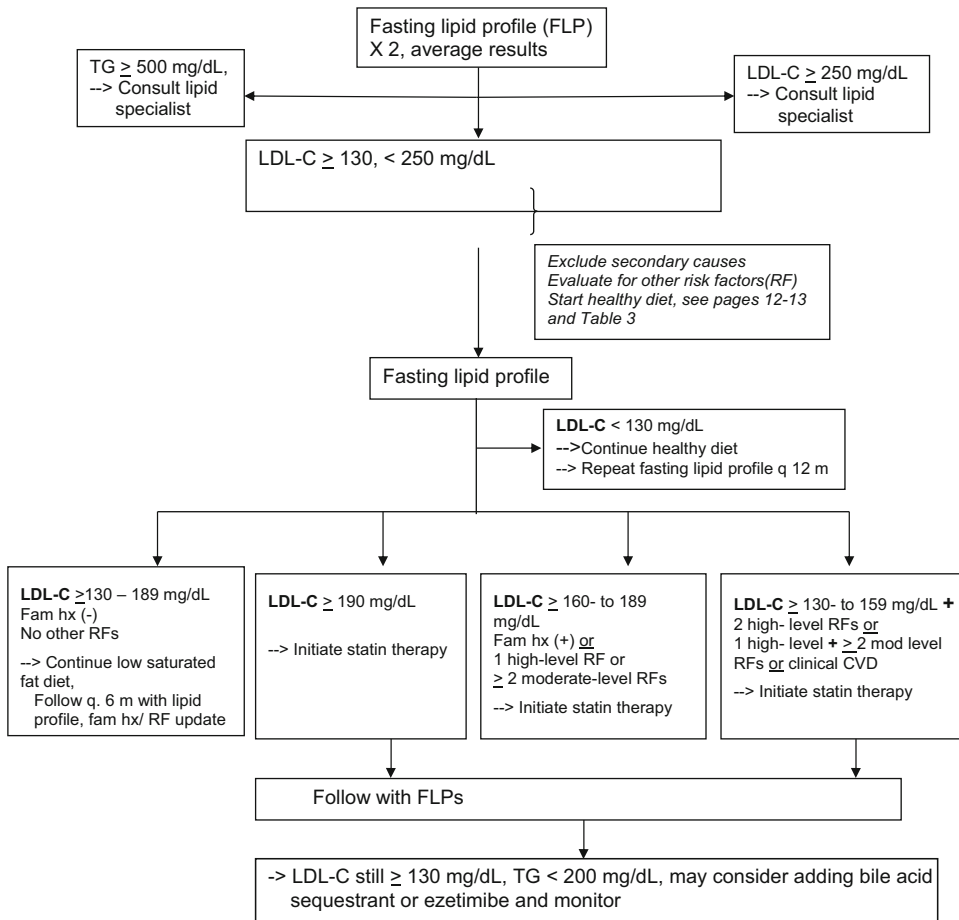
In childhood, pharmacologic treatment for elevated triglycerides is only considered as prevention of pancreatitis and after failed dietary management. Generally, triglyceride levels repeatedly >500–750 mg/dl are treated. Fish oil (4 g) is used initially, and fibrates are considered only in severe cases; there are no clinical trials of fibrate use in childhood.

There are no indications for treatment of low HDL cholesterol in children.

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## Tobacco Use

Tobacco use remains the most important preventable cardiovascular risk factor in children (Anonymous 2012). In the United States, after years of decline, adolescent tobacco use spiked reaching a peak in the mid- to late 1990s. Tobacco use then declined until about 2002–2003 without further improvement. About 25% of high school students currently describe themselves as having smoked at least one cigarette in the last month (Garrett



**Fig. 3** Management of high LDL cholesterol (target LDL-C)

et al. 2011). The college age range has the highest tobacco use. Tobacco use rates are monitored by an annual youth behavior risk survey and are available from the Centers for Disease Control.

Risk factors for tobacco use are family smoking, peer group smoking, lower socioeconomic status, presence of problem or antisocial behaviors, and susceptibility to media campaigns or influences with regard to tobacco use (Anonymous 2012; Elders et al. 1994). Cigarettes, because of nicotine, are highly addictive. It is estimated that smoking 100 cigarettes or less may be sufficient to become an addicted smoker. E-cigarettes may be a gateway to tobacco use (Barrington-Trimis et al. 2016). Though randomized trials suggest physicians can be effective in smoking cessation treatment, success rates are

low, particularly in youth (Anonymous 2011). Pharmacologic treatments are available, but there is limited published experience in youth. Though adolescents frequently attempt to quit smoking, these efforts generally occur outside the setting of supervision by healthcare providers or other experienced counselors. The presence of tobacco use may be an indication for intensification of management of other risk factors.

A history of tobacco use should be sought in every adolescent, particularly if a cardiovascular risk factor is present since the combination of tobacco use with another major risk factor is probably the most common and malignant setting for multiple risk (Anonymous 2011). Since most pediatric healthcare providers are inexperienced in smoking cessation treatment, referral to a

smoking cessation program or telephone quit line should be considered.

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## Diabetes Mellitus

In adults, diabetes mellitus is considered a vascular disease equivalent (Anonymous 2001). Cardiovascular disease is the leading cause of death in diabetics. Accelerated atherogenesis is present in both type 1 and type 2 diabetes. Diabetes is the only risk factor to erase the gender protection of about 5–10 years in atherosclerosis development in women (McGill et al. 2008). Studies of children with type 1 diabetes mellitus have shown increased carotid IMT; cardiovascular risk factors and age at onset of diabetes influence carotid IMT measurement (De Ferranti et al. 2014; Maahs et al. 2014). Cardiovascular risk factors are highly prevalent in children with type 2 diabetes mellitus and progress during the course of the illness (Anonymous 2013a, b; Maahs et al. 2014).

The prevalence of both type 1 and type 2 diabetes mellitus is rising, the latter because of the obesity epidemic. In adolescents, new cases of type 2 diabetes mellitus are now almost as common as type 1 (Dabelea et al. 2007).

There is currently little published experience with cardiovascular risk factor control in childhood diabetes. However, consensus recommendations consider the presence of diabetes an indication for intensification of management of cardiovascular risk factors (Anonymous 2003a). Studies in adults suggest significant cardiovascular event reduction rates, similar to those in non-diabetics, can be achieved with hypertension and lipid-lowering treatment (Anonymous 2001).

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## Obesity, Family History, Gender, Nutrition, Physical Activity, Socioeconomic Status, Ethnic Diversity, and the Evolution of Cardiovascular Risk

A number of factors contribute to the evolution of cardiovascular risk in childhood. Some of these, such as family history, physical inactivity, and low

socioeconomic status are also independent risk factors for cardiovascular disease. Psychosocial stress likely predisposes to adverse risk exposure (Gidding and Sood 2015). From an evidence and research standpoint, it is often more difficult to directly relate these factors to cardiovascular events and intermediate measures of end-organ injury. However, it is also clear that optimal health habits are critical for primordial prevention, the prevention of risk factor development in the first place.

The development of obesity is the most important pediatric public health problem today. Worsening obesity is the most important cause for the transition from the relatively low-risk state of childhood to the presence of cardiovascular risk in adulthood, particularly for the development of hypertension, diabetes mellitus, and the high triglyceride/low HDL cholesterol phenotype (Steinberger and Daniels 2003). The presence of obesity-associated multiple risk tracks into adulthood and, in one preliminary study, is associated with premature adult morbidity including diabetes (Morrison et al. 2008). Nonetheless, the prevention of obesity development in at-risk infants and children and the prevention of worsening obesity in affected children and adolescents is an important part of regular pediatric practice as at least one third of US children are overweight or obese. Longitudinal data following children into adulthood suggests that obesity control will restore cardiovascular health while excess weight gain will substantially worsen risk (Juonala et al. 2011).

Family history remains an independent risk factor for atherosclerosis (O'donnell 2004). In adults, a positive family history increases risk even after control for potential genetic traits. Positive family history predicts risk in offspring; conversely risk in childhood predicts risk in related adults. Family history independently predicts the presence of subclinical atherosclerosis (Gaeta et al. 2000; Wang et al. 2003). Therefore, the presence of a positive family history of atherosclerosis-related disease or risk factors should prompt evaluation of family members for both genetic and environmental risk factors for intervention.

For all risk factors, there are gender-related differences in expression. In general, atherosclerosis develops about 5–10 years later in women than men (Mcgill et al. 2008). However, atherosclerosis-related diseases remain the leading cause of death for women. Two risk factors impact the protective relationship of gender for women: diabetic women do not have any difference in the age-related onset of atherosclerotic complications, and the use of tobacco obliterates the 5–10 year protective effect.

Nutrition has a significant impact on the evolution of cardiovascular risk. A lifelong low cholesterol, low saturated fat diet has a small but significant effect on lipid levels and blood pressure (Niinikoski et al. 2007). A diet low in salt is associated with lower blood pressure (He and Macgregor 2006). Though the equivalent of the DASH study has not been performed in children, it seems reasonable to generalize the findings of that study to children as foods recommended in the DASH diet are nutrient dense and important for growth and development (Gidding et al. 2005). Excess caloric intake causes obesity.

Higher levels of physical fitness are associated with a small but significant effect on blood pressure and protects against the future development of obesity, hypertension, metabolic syndrome, and diabetes mellitus (Carnethon et al. 2003; Kelley et al. 2003). It is likely that an above average level of activity reduces the rate of rise of blood pressure over time (Gidding et al. 2006a).

Socioeconomic status and psychosocial stress play an important role in the evolution of cardiovascular disease risk, particularly with regard to behavioral factors (Gidding and Sood 2015; Lynch et al. 2006). Risk factor rates, particularly obesity-related comorbidities and tobacco use, are much higher in groups with lower socioeconomic status. Many factors may play a role: lower educational level, less access to preventive care, lower literacy rates making comprehension of health-related messages more difficult, targeting of lower class groups for marketing of less healthy products (tobacco, fast food), less trust in physicians and health-related messages, and barriers to access to healthier nutrition.

Most data on cardiovascular disease has been acquired in Caucasian populations, particularly male. Though comparative studies across nationalities, cultural groups, and ethnic groups suggest that cardiovascular risk factors are the same in all groups, the importance of each risk factor and the expression of risk factors in relationship to environmental stress may be different. For example, factors related to the metabolic syndrome arise at different levels of body mass index in different ethnic groups (Razak et al. 2007). The prevalence of specific risk factors also varies by ethnic group (Winkleby et al. 1999). Thus, more research is necessary before cardiovascular disease prevention recommendations can be made more specific for particular cultures.

### Nontraditional Risk Factors

A number of factors, different from the major risk factors described above, have been identified that at least in some studies have an independent contribution to cardiovascular risk. These fall into several groups: measures of intermediate end-organ injury and/or subclinical atherosclerosis, markers of inflammation, and physiologic measures that may be implicated in atherogenesis. In adults, an algorithm has been established for determining if these nontraditional risk factors substantially improve risk prediction beyond that provided by the major risk factors described previously in this chapter (Greenland et al. 2010). Though some research on these factors has been done in children, it is often cross sectional and is insufficient to add to clinical assessment outside of a research setting.

The most important marker of end-organ injury is echocardiography to assess left ventricular mass and left atrial size (Gidding 2007). These measures are correlated with hypertension and obesity, and independent relationships to cardiovascular morbidity are well established (Gidding et al. 2013). Subclinical atherosclerosis assessments including CT scanning to assess for coronary calcium and cIMT are not useful clinically in children (Urbina et al. 2009). Calcium does not enter atherosclerotic lesions until young

adulthood, and normal values for cIMT are age and operator dependent and have not been established (Gidding 2007). Assessment of brachial reactivity using ultrasound techniques has provided insights into the presence of endothelial injury early in life, particularly with regard to tobacco exposure and the benefits of exercise; however, these studies do not yet have independent value in clinical practice beyond conventional risk factor assessment (Celermajer 2008; Roman et al. 2006). Pulse wave velocity correlates with the presence of elevated blood pressure, diabetes, physical inactivity, and obesity (Urbina et al. 2012).

In adults, the best studied marker of inflammation is c-reactive protein; others include various vascular adhesion molecules and inflammatory cytokines (Ridker 2007). There is very little pediatric data on these factors and for many, pediatric levels may be different than in adults (Balagopal et al. 2011). There is limited information on tracking, measurement variability, and relationship to adult intermediate endpoints. Obesity and atherosclerosis are pro-inflammatory; these measures can be considered markers of ongoing physiologic processes associated with obesity and the other major risk factors (Rasouli and Kern 2008). Inflammatory and metabolic mechanisms associated with atherosclerosis development in adults are present in youth. In African-Americans, when adults and adolescents are stratified by c-reactive protein level or triglyceride/HDL ratio, they have similar levels of body mass index and waist circumference suggesting inflammatory and metabolic mechanisms associated with atherosclerosis development in adults are present in youth (Deloach et al. 2014; Gidding et al. 2015b). Limited trial data suggests adverse biomarker profiles can be ameliorated by diet and/or exercise. Currently, evidence is insufficient to add these markers to clinical assessment outside of a research setting (Urbina et al. 2009)

There are diverse physiologic measures that may improve risk assessment by a small amount. Examples include urinary albumin excretion (a measure of renal vascular injury), fibrinogen (a marker of the prothrombotic state but well correlated with obesity), adiponectin and leptin

(hormones associated with obesity), and homocysteine (associated with accelerated atherosclerosis when extremely elevated in genetic conditions). An additional physiologic factor under intense scrutiny is low birth weight, though the mechanisms of this relationship are beyond the scope of this review (Norman 2008).

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## Summary

Atherosclerosis begins in youth. The major risk factors for the development of premature atherosclerosis are hypertension, dyslipidemia, tobacco use, and diabetes mellitus. For some individuals, genetic and other predisposing conditions may cause a high-risk state in childhood. For the general population diet, physical activity, family history, obesity, and low socioeconomic status contribute to the development of risk factors. For most children with identified risk factors, behavioral management is critical to prevent worsening of risk. For children at extremes of the risk distribution or with multiple risk factors, pharmacologic treatment may be necessary.

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## Cross-References

- ▶ [Diagnostic Evaluation of Pediatric Hypertension](#)
- ▶ [Epidemiology of Primary Hypertension in Children](#)
- ▶ [Hypertension in Children with Type 2 Diabetes or the Metabolic Syndrome](#)
- ▶ [Obesity Hypertension: Clinical Aspects](#)
- ▶ [Value of Routine Screening for Hypertension in Childhood](#)

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**Part III**

**Hypertension in Children: Etiologies  
and Special Populations**

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## Abstract

While young children likely have no differences in BP related to race/ethnicity, emerging data suggest that, at least in older children, race and ethnicity may be important factors influencing blood pressure. Blood pressure in children is still assessed using normative data from the National High Blood Pressure Education Program which include adjustment for an individual's age, gender, and height. These current blood pressure threshold values are derived from a multiethnic sample of children but do not employ ethnicity specific thresholds for childhood blood pressure. In this chapter, we review the evidence for ethnic differences in childhood blood pressure, including childhood ambulatory blood pressure, and discuss some of the potential mechanisms behind these differences.

## Keywords

ABPM • Blood pressure • Children • Ethnicity • Hypertension • Minority • Race

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## Introduction

Blood pressure (BP) differences between various ethnic groups are well described in the adult population (Ong et al. 2006; Wright et al. 2011). Large, cross-sectional studies have demonstrated that, per capita, minority ethnic groups have both a higher prevalence of hypertension and more frequent and severe end-organ damage and outcomes (Guo et al. 2012; Hajjar 2003; Egan et al. 2014). Although a growing body of evidence indicates that differences in blood pressure parameters

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between Black and White children appear during adolescence (Daniels et al. 1998b; Rosner et al. 2009; Wang et al. 2006; Theodore et al. 2015), the cause of these differences and when they develop in childhood is yet to be fully determined.

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## Racial and Ethnic Variation Among Adult Hypertensives

Worldwide, Black adults have not only the highest prevalence of hypertension but also more severe hypertension, more hypertensive target organ damage (TOD), and perhaps an earlier onset of hypertension (World Health Organization 2013). These findings are clearly true for Blacks in the United States (Kramer et al. 2004; Holmes et al. 2013; Fuchs 2011; Jones and Hall 2006). The National Health and Nutrition Examination Survey (NHANES) has consistently demonstrated that non-Hispanic Blacks in the United States have a higher prevalence of primary hypertension, particularly severe hypertension (>180/100 mmHg) which is over eight times more prevalent in Blacks than in other ethnic groups (Guo et al. 2012). The American Heart Association 2015 scientific report notes that Blacks in America continue to be at increasing risk for primary hypertension and are more than twice as likely to die of heart disease compared with Whites (Havranek et al. 2015). Worse, the CDC continues to issue poor report cards on the control of hypertension in the United States, with fewer than half of patients adequately treated to target blood pressures (CDC 2012). Although poorly controlled hypertension is rampant across all segments of society, a recent MMWR from the CDC reports that Blacks (57.0%) and Hispanics (63.1%) are significantly more likely to have uncontrolled hypertension compared to their White (51.5%) counterparts ( $p < 0.001$ ) (Gillespie and Hurvitz 2013).

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## Do Racial Differences in Blood Pressure Begin in Childhood?

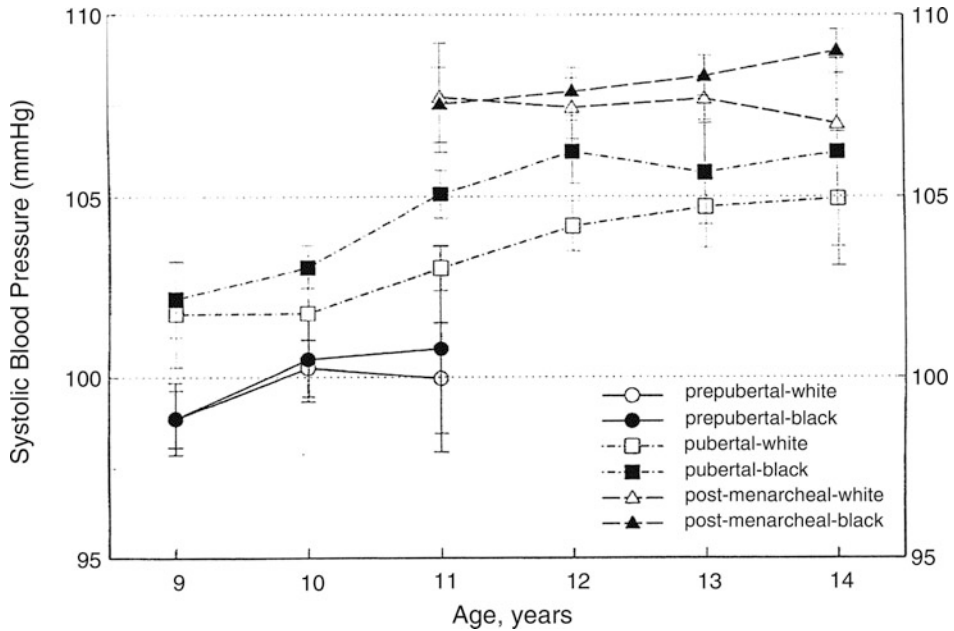
Though agreed upon as established in adults, the emergence of ethnic differences in blood pressure during childhood is more controversial. None of

the pediatric guidelines, including the 2004 National High Blood Pressure Education Program's (NHBPEP) Fourth Report, offer separate normative values for children of varying ethnic backgrounds (NHBPEP 2004). The samples from which pediatric normative BP values are derived include children from multiple ethnic and race backgrounds. Though height, age, and gender all are accounted for in the determination of pediatric normative BP values, ethnicity is not included as significant factor influencing BP. This lack of ethnicity specific normative data is likely due to race and ethnicity often being confounded with other known determinants of pediatric BP variability such as body size, sexual development, and socioeconomic status.

Rosner and colleagues have analyzed the NHBPEP data used to generate the pediatric normative BP values on several occasions to assess whether ethnicity is a factor influencing BP (Rosner et al. 2000; Rosner et al. 2009). Their initial analysis in 2000 (Rosner et al. 2000) included 47,196 children aged 5–17, including 29,730 White and 17,466 Black subjects. The only significant racial differences found were modified by body size, specifically BP was elevated in obese White males versus obese Black males but among normal weight children Black males had higher BP versus White males. The authors concluded that due to the substantial height and weight variations between racial groups, body size rather than race was the primary factor underlying observed BP differences. They determined at that time that separate norms by ethnicity were unwarranted.

In 2009, Rosner's group reanalyzed a larger dataset, adding both children under age 5 years and Hispanics to the dataset. The resulting analysis included BP data from 58,698 children 1–17 years old (Rosner et al. 2009). This secondary analysis concluded that while BMI did strongly influence BP, there are definite racial differences in BP that could not be fully explained by anthropometrics alone. These effects included particularly high BP in Hispanic boys of all sizes.

Even before these analyses of the NHBPEP data, Daniels in 1996 demonstrated significant differences in BP between 9- and 10-year-old Black and White girls (Daniels et al. 1996). The



**Fig. 1** Mean systolic blood pressure (mmHg) by age, sexual maturation stage, and race (From Daniels (1998) *Hypertension* 31:101 (Daniels et al. 1998b) with permission)

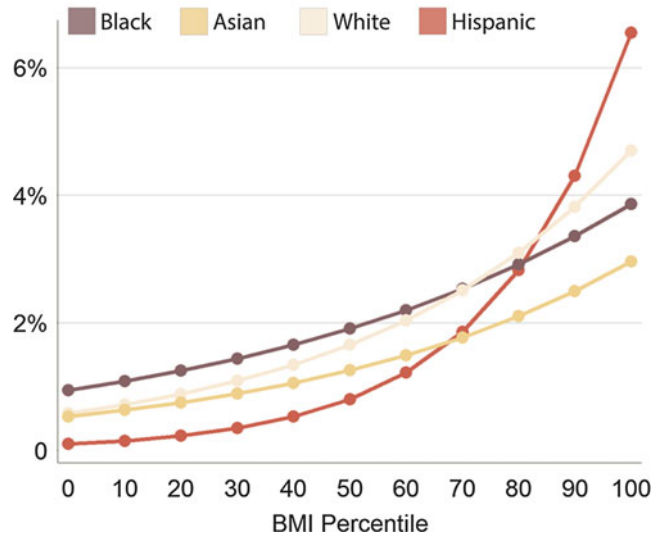
NHLBI Growth and Health Study (NGHS) evaluated 1,213 Black and 1,166 White girls and found the Black girls had higher BP (102/58 vs. 100/56). Interestingly, though matched for age, the differences in blood pressure were found to be related to sexual maturity, which began earlier in the Black girls (Daniels et al. 1998b). In a subsequent analysis, this same cohort was followed through age 14 with annual measurements of height, weight, BP, and sexual maturity rating. The average BP in the Black girls remained ~2 mmHg higher than their White counterparts (see Fig. 1) (Daniels et al. 1998b). Although race was found to be a significant predictor of increased BP, additional significant factors included age, sexual maturation, height, and BMI. At all stages of sexual development, Black girls demonstrated higher BP.

Muntner used cross-sectional NHANES III data, gathered between 1988–1994 and 1999–2000, to assess trends in BP among US children and teens aged 8–17 years (Muntner 2004). He reports that in 1999–2000, non-Hispanic Black youth had higher SBP than non-Hispanic White youth. The differences were more pronounced between ethnically diverse boys

(2.9 mmHg) than for girls (1.6 mmHg). Updated NHANES analysis from Rosner in 2013 saw similar trends with non-Hispanic Black youth having higher rates of elevated blood pressure compared to non-Hispanic White and Mexican-American youths (Rosner et al. 2013).

Houston-based blood pressure screening has been ongoing since 1978 with early cohorts included in the NHBPEP normative data (Gutgesell et al. 1981). Recent school-based screening studies have continued to gather information on blood pressure and now include over 20,000 children aged 10–19 years participating since 2000 (Cheung et al. 2017). Overall prevalence of hypertension in these children is 1.7% in Asians, 2.6% in Whites, 2.7% in Blacks, and 3.1% in Hispanics. Again, these racial differences in hypertension prevalence can be partially explained by higher BMI in Black and Hispanic children but the relationship between BMI and hypertension varies significantly between race and ethnic groups. Specifically, Hispanic children in Houston have dramatically increased rates of hypertension at higher BMI percentiles compared to all other racial groups (see Fig. 2).

**Fig. 2** Average prevalence of sustained hypertension by BMI percentiles for four race/ethnic groups based on school-based blood pressure screenings in over 20,000 children aged 10–19 years in Houston, TX (From Cheung et al. 2017)



Ethnic differences in BP between boys and girls have also been seen in studies conducted outside of the United States. In the United Kingdom, Harding and colleagues followed a multi-ethnic population of 6,643 teens in the Determinants of Adolescent Social Well-Being and Health (DASH) study (Harding et al. 2006b). Although children self-reporting as of Black African origin (distinguished in their cohort from Black Caribbean subjects) were more overweight and more socioeconomically disadvantaged, Harding reports no initial difference in BP in early adolescence (Harding et al. 2006b). At age 12, SBP did not differ by ethnicity for either boys or girls. Subsequent longitudinal assessment of the cohort through age 16 revealed emergence of SBP differences in boys (Harding et al. 2010). The increase in BP was more pronounced in Black African boys compared to Whites, resulting in 2.9 mmHg greater systolic pressures. In the girls, however, ethnic differences in BP did not develop despite the increasing BP in Black girls and relatively flat BP trends in White girls. Diastolic BP differences were even more pronounced, particularly in the boys. Although the DBP increased over time in White boys (65.5–67.0 mmHg), the increase was even greater among Black boys (65.3–68.3 mmHg,  $p < 0.05$  compared to White subjects).

As a small minority group in the United States compared to Blacks and Hispanics, Asian children are often underrepresented in studies of childhood blood pressure. A few studies have specifically compared blood pressures between Asian children and children of other ethnicities. One study from 1986 found Asian girls to have elevated SBP and boys elevated DBP compared to other children (Hohn et al. 1994). Harding also showed that South Asian girls showed the strongest positive association of blood pressure with BMI, waist circumference, and early puberty (Harding et al. 2006a). A recent chart review by Lo et al. of nearly 200,000 children aged 3–17 years showed that Black and Asian children had the highest prevalence of confirmed hypertension (Lo et al. 2013). Despite these findings, most studies including Asian children have found either no significant differences in BP compared to White counterparts or have found a lower risk of hypertension compared to other ethnic groups (Kmietowicz 2015; Lee 2014; Madrigal et al. 2011).

## Hispanics and Ethnic Differences in BP

Most discussions of racial or ethnic differences in blood pressure have focused on non-Hispanic Blacks compared to Whites. Although a historically underrepresented group in epidemiologic studies,

Hispanics accounted for 56% of population growth in the United States between 2000 and 2010. In 2011, the median age of Hispanics in the United States was 27.6 years old compared to 42.3 years for non-Hispanic Whites (Hixon et al. 2012). Because Hispanic-Americans are substantially younger than other racial and ethnic groups, adult surveys often underestimate the burden of hypertension in Hispanics, who as a population in the United States have yet to reach the typical older age of hypertension onset. Recent NHANES adult data show Black males to have the highest prevalence of hypertension at 37.8%, while Hispanics and Whites have similar rates of 22.1% and 26%, respectively. Additionally, hypertension prevalence has increased from 1998 to 2008 in adults for all racial groups except for Hispanics (Guo et al. 2012; Egan 2010). Despite similar rates of hypertension, effective control of hypertension in Hispanics, particularly young Hispanics, is often the lowest out of all ethnic groups. National studies have shown that Hispanics aged 20–39 have the lowest knowledge of, therapy for, and control of their hypertension (Guo et al. 2012; Al Ghatrif et al. 2011). Due to the emerging demographic of younger age in the Hispanic population, it is only through the examination of children and young adults that the true prevalence of hypertension in Hispanics can be uncovered. These analyses will provide insight into the forthcoming hypertension trends in America as this population ages.

Earlier studies such as one by Barón in 1986 showed that Mexican-Americans had comparable BP to both Blacks and Whites despite Black females being significantly heavier than other groups (Baron et al. 1986). With the rising proportion of Hispanics in the young population, recent studies in children have shown that compared to non-Hispanic Whites, Hispanic youths have an increased prevalence of hypertension that differs by gender and is strongly tied to obesity. National surveys of 8–17 year-olds from 1963 to 2002 have concluded that an ethnic gap in high BP appeared in 1999 where both non-Hispanic Blacks and Mexican-Americans had the highest prevalence of HTN compared to non-Hispanic Whites (Din-Dzietham et al. 2007). In 2006, Jago and colleagues showed that both Blacks and Hispanics had increased rates of

elevated BP. Among boys, the highest rate of elevated BP was seen in Blacks, while Hispanic girls had higher rates of elevated BP compared to both Blacks and Whites, after controlling for other covariates (Jago 2006). The largest, most nationally representative study of BP in children did find significantly higher prevalence of elevated SBP and DBP in normal and overweight Hispanic compared to White boys. Any differences of BP by race in girls were explained fully by BMI (Rosner et al. 2009; Din-Dzietham et al. 2007).

Our data from the UT-Houston screening program over the last 12 years has shown that the highest rate of hypertension is among adolescent, obese, Hispanic boys at 9.2% (Cheung et al. 2017). This trend is consistent with our concurrent finding that Hispanic boys of all ages have the highest rate of obesity at 27.5% compared to either Black (20.1%) or White boys (16.1%). These higher rates of obesity might largely explain the emerging trend of increased hypertension in Hispanics. The relationship between obesity and blood pressure may be more pronounced in non-Black populations. Klimentidis showed in 2012 that among Hispanic Americans and European Americans, higher total body fat is strongly associated with higher SBP. Among Blacks, however, total body fat is not in the best fitting model to describe BP variability (Klimentidis et al. 2012). Chen used large NHANES data to also demonstrate that significant Black-White differences in BP were only found in boys with normal body size (OR = 2.16; 95% CI: 1.22–3.80; P = 0.008), but not among those who were overweight or obese (Chen et al. 2015).

Additionally, Houston is not the only locality to demonstrate the increasing burden of obesity on Hispanic youth. National surveys performed in children during 2008 have shown that the largest increase of obesity was in Mexican-American boys to 26.8% obese and in non-Hispanic Black girls to 29.2% (Ogden et al. 2006; Li et al. 2010). A more recent analysis from 2012 has shown that, unfortunately, Black boys have now “caught up” and have even overtaken Hispanic boys in obesity rates (21.2% Hispanic vs. 24.3% non-Hispanic Black) (Ogden et al. 2012). Both of these groups have significantly higher proportion of obesity compared to

Whites (14.0%). Although the link between childhood obesity and elevated blood pressure is clear (Flynn and Falkner 2011; Freedman et al. 2007; Sorof and Daniels 2002; Sorof et al. 2004; Flynn 2013), other factors discussed below may also play a role in the development of early hypertension.

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## Origins of Ethnic and Racial Differences

As in adults, the predominant diagnosis in teens with elevated blood pressure is primary (essential) hypertension. While deemed primary hypertension, there are several social and physiological factors that likely influence the severity and unequal racial distribution of high blood pressure such as obesity, socioeconomic level, geographic location, and genetic traits.

Certainly there are socioeconomic differences between ethnic groups in the United States which might confound the relationship between blood pressure and race/ethnicity. Since minorities are more likely to have many indices of lower socioeconomic status (SES), some of the apparent association between BP and ethnicity might instead be explained by SES. The United States Department of Health and Human Services reported that from 1988 to 1994 the prevalence of hypertension was 26–27% for poor or near poor men while only 22% in men from more affluent background (Izzo and Black 2008). People at lower SES are more likely to have unhealthy diets and less likely to possess advanced education or be able to afford access to preventative health care. Conversely, other data indicate that SES is positively associated with SBP only among Blacks. Amerindian and African admixture are negatively associated with SBP, whereas perceived racial discrimination and SES are positively associated with SBP (Klimentidis et al. 2012).

Obesity in the United States is related to both SES and geographic location. Over half of the Black population in the United States resides in the Southeastern states (Izzo and Black 2008; Flack et al. 2008). Local differences in diet and lifestyle in these 13 Southern states may explain some of the BP differences between Blacks and

Whites. Kiefe found that both Blacks and Whites from Birmingham had a much higher incidence of hypertension than those from Chicago or Oakland, although within Birmingham, Blacks continued to have higher BP than Whites (Kiefe et al. 1997). McGrath looked at individual and neighborhood race and SES effects on ambulatory BP to show that race only explains higher DBP in Black versus White adolescents, while SBP was explained by neighborhood SES (McGrath et al. 2006). Conversely, higher sleep BP values are not seen just in African-Americans but also in recent African immigrants suggesting a biological, not societal, factor influencing elevated nocturnal BP in Blacks (Osei and Schuster 1996).

Diet is another important factor in BP regulation that varies across both SES and ethnic groups. The Treatment of Mild Hypertension Study (TOMHS) (Neaton 1993) assessed baseline dietary sodium intake by measuring urinary excretion of  $\text{Na}^+$  and  $\text{Na}^+:\text{K}^+$  ratio. The study reported that discrepant levels between Blacks and Whites correlated with differences in SES (Mascioli et al. 1990). Specifically, higher urinary  $\text{Na}^+$  excretion was found in Blacks at lower SES and education, but not Whites (Ganguli 1997). Using NHANES data from 1988–2008, Rosner et al. showed that while Black youths had higher BP overall, sodium intake was associated with elevated BP only in non-Black youths but not in Black youths (Rosner et al. 2013). Prather et al. further demonstrated the importance of diet by showing that after randomization to a DASH diet, Blacks had significantly increased nocturnal SBP dipping compared to those on a control diet. While Black subjects had severely diminished SBP dipping at baseline compared to Whites, no ethnic differences in SBP dipping were found following the DASH diet intervention (Prather et al. 2011). Using a transition from low-salt to high-salt diet in Black adolescents, Wilson showed significantly less BP dipping in subjects who were sensitive to salt. Fifty percent of the salt-sensitive subjects were nondippers (<10% decrease in wake to sleep BP) compared to only 5.4% of the salt-resistant subjects for diastolic BP and 18.9% of the salt-resistant subjects for mean BP (Wilson 1999).

Another theory regarding difference in adolescent and adult blood pressures relates to birth weight and early postnatal growth. Low birth weight for gestational age has been associated with eventual higher BP in several studies. Huxley performed a systematic review and meta-analysis of the role of low birth weight and eventual adult HTN and showed that adult blood pressure fell with increasing birth weight; the size of the effect was approximately 2 mmHg/kg (Huxley et al. 2000). Additionally, subjects with the highest BP were those with the greatest “catch-up” growth or those subjects of low birth weight but high rates of subsequent growth. Lending weight to that theory, Cruickshank evaluated this hypothesis using a subset of data from the Bogalusa Heart Study (Cruickshank 2005). In a carefully controlled analysis of 148 children, they found that birth weights were a mean of 443 and 282 g lower among Black boys and girls, respectively, than their White counterparts. Despite their smaller start, Black children had greater early postnatal growth. By age 4–5, the weights and heights of the boys were equal, but Black girls had actually overtaken the White girls in both weight and height. By their teen years, the White boys were both taller and heavier than the Black boys, yet despite their smaller size, the Black boys had BP that was 3.4/2 mmHg higher. At least in that analysis, differences in adolescent BP were mostly explained by the initial smaller weights of the minority infants and further explained by their more rapid early postnatal growth that surpassed that of White babies. These early size differences between races were more important in predicting adolescent BP than concurrent stature. Conflicting longitudinal data from Falkner failed to demonstrate a convincing relationship between low birth weight and adolescent BP (Falkner et al. 2003).

Much effort has gone into establishing the mechanism of primary hypertension. One mechanism seems to involve a pathologic response to physiological stress. Early studies revealed that while both Black and White subjects demonstrated an increased sodium excretion in response to competitive mental stressors, natriuresis was blunted in Black subjects (Light and Turner 1992). This altered response results in a pronounced

stress-induced sodium retention. More recently, Harshfield has confirmed the marked reduction in this response in Black teens compared to White subjects (Harshfield 2002; Harshfield et al. 2002a). When 118 Black youth were physiologically challenged, they had a greater increase in BP and a more delayed return of BP to prestress levels. The blunted excretion of sodium and resultant BP elevations might explain not only Black patients’ improved responses to diuretics but also some of the increase in BP loads experienced by Blacks when assessed with 24 h ambulatory blood pressure monitoring (see below).

Timing of sexual maturity has been shown in some studies to be an important mechanism behind blood pressure increases in children but a few studies examine these associations between racial groups. Harding et al. demonstrated the relationship between blood pressure and early puberty in girls from South Asia but without comparison other groups (Harding et al. 2006a). The NGHS did evaluate both Black and White girls to show that early sexual maturity was seen more in Black compared to White girls. This earlier puberty status was shown as a significant factor behind the higher blood pressures observed in Black girls, even after matching with White counterparts by age (Daniels et al. 1998b).

Age and body size are perpetual confounders in the field of pediatric hypertension. While older, taller, and heavier children have higher BP, height, and weight patterns distribute unevenly across racial/ethnic groups and genders. One of the first studies showing racial/ethnic BP variations by Harshfield in 1989 showed increased daytime SBP in both male and female Blacks and increased nocturnal SBP and DBP in Black males. Mean nocturnal SBP was 105 mmHg for White girls and 105 mmHg for Black girls but significantly higher for Black boys at 112 mmHg compared to 106 mmHg for White boys. Though concerning, these results are confounded by age since the Black population in this study was significantly older than the White population (Harshfield et al. 1989).

In addition to differences in body size, ethnic groups demonstrate unequal maturation as assessed by bone age. Russell reported skeletal



maturation to be more advanced in Blacks compared to Whites (Russell et al. 2001). These Black children were also more obese compared to White children. Pludowski performed a similar analysis of bone age in hypertensive children and BMI matched controls. Hypertensive children had significantly advanced bone age compared to chronologic age (Pludowski et al. 2009). These differences between bone age and chronologic age were more pronounced with increasing blood pressure stages.

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### **Racial and Ethnic BP Differences by Ambulatory Blood Pressure Monitoring**

Ambulatory blood pressure monitoring (ABPM) has been proven to be a more precise measure of BP than casual measures. ABPM can detect masked or white-coat hypertension and correlates more strongly to evidence of target organ damage than clinical BP measurements (Flynn and Urbina 2012; Lurbe et al. 2005; McNiece et al. 2007b; Sorof 2001; Sorof et al. 2002). Moreover, ABPM is an essential, cost-effective tool in the evaluation of diurnal variations in BP and has been recommended as an adjuvant to diagnosis of hypertension in selected pediatric populations (NHBPEP 2004; Flynn et al. 2014). There is emerging evidence that, like other measurements of BP, ambulatory BP patterns differ between ethnic groups. A meta-analysis in adults has shown elevated ambulatory SBP and DBP during both days and nights in Blacks compared to Whites (Profant and Dimsdale 1999).

Most studies in children have also found evidence that ambulatory BP varies by race. A particularly common finding is blunted nocturnal dipping in Blacks compared to Whites. One of the earliest studies by Harshfield examined Black and White children from Memphis, TN, and Augusta, GA, and found that Black children had reduced nocturnal decline in both SBP and DBP that remained significant after controlling for height (Harshfield et al. 2002c). Although age was not a significant factor in multivariate analysis, the

Black children were slightly older in the Memphis population, which could account for higher mean BPs but should not have affected the dipping profiles. In an extension study of the same cohort from Augusta, whose ages were comparable between races, follow-up ABPM showed that ambulatory BP values were consistent during a 2-year follow-up. Nocturnal decline in SBP was blunted for Blacks compared to Whites at the follow-up visits. Specifically, nocturnal decline was <10 mmHg on both occasions in 32% of Blacks compared with only 14% of Whites (Harshfield et al. 2002b).

Belsha examined 54 normotensive subjects and 45 untreated, mildly hypertensive subjects aged 6–17 years. This study found nocturnal SBP fall to be reduced in Blacks compared to Whites (Belsha et al. 1997). In a study that spanned childhood through young adulthood, Wang measured a 24 h ambulatory BP up to 12 times per subject over a 15-year period in 312 Blacks and 351 Whites aged 7–30 years old. BP increased with age for all races, but Black subjects had consistently higher daytime SBP and DBP at all ages. For nocturnal SBP and DBP, the difference between Black and White means began to increasingly widen after the age of 10. While family history of hypertension explained much of the racial differences in daytime SBP, it did not explain why Blacks had overwhelmingly higher average SBP and DBP at night compared to Whites (Wang et al. 2006).

Aguilar studied ABPM results in 43 clinically normotensive, obese children aged 7–17 years and showed that multiple ambulatory BP measures correlated to BMI z-score but not to race (Aguilar et al. 2010). Although this study showed no significant ethnic differences, it is likely that with only 43 subjects, this study was underpowered to detect a racial difference. Kapuku noted differences in 24 h, day, and night SBP while also showing height, weight, and BSA differences in race as well. While their final analysis controlled for body size and BP effects on cardiac outcomes, it is not known whether the racial differences in body size fully account for the SBP differences (Kapuku et al. 1999). Li did repeated ABPMs up

to 12 times on Black and White Americans starting at 14 years old. Boys had steeper increases in BP with age compared to girls and Blacks had higher blood pressure variability than Whites. BMI and waist circumference were related both to blood pressure variability and to race. These factors confound the apparent association such that after controlling for either BMI or waist circumference, race was no longer a significant predictor of BP variability (Li et al. 2010).

It is important to note that most of these studies of ABP in children compare actual SBP and DBP mmHg without standardizing or classifying hypertensive status. Current ambulatory BP normative thresholds are based on a cohort of exclusively White, Central European children that did not include any ethnic variation (Soergel et al. 1997; Wühl et al. 2002). Despite the ethnic and racial differences in BP and target organ damages described in this chapter, minority children were completely unrepresented in establishing ambulatory BP normative thresholds currently in use. Ambulatory BP values in varied racial groups are thus presently unknown and the application of current normative thresholds to a multiethnic setting is likely faulty. An alternative method, used by Brady, was to employ clinical BP thresholds from the 2004 NHBPEP Fourth Report to standardize ambulatory BP values collected in a multiethnic population (Brady et al. 2010; NHBPEP 2004). Brady controlled for gender, age, and height by dividing ambulatory BP means by Fourth Report 95% percentile values and found elevated daytime values in Blacks for both SBP and DBP as well as elevated 24 h systolic loads. While the use of FR normative data is most appropriate for daytime value comparison, their use could provide some ability to standardize samples that vary by gender, age, and height. The true values that should be applied in the assessment of ambulatory BP thresholds are the levels that predict hypertensive target organ damage. Though these exact thresholds are unknown, it is clear that children with hypertension based on current thresholds do develop target organ damage (McNiece et al. 2007a).

## Ethnic Differences in BP-Related Target Organ Damage in Children

While it is well known that Black adults in the United States have the most severe hypertension, target end organ damage (TOD), and cardiovascular events (Guo et al. 2012), data on the effect of hypertension on target organ damage in minority children are less clear. One paper suggests that childhood hypertension is in fact related to premature death, at least in some ethnic populations such as Native Americans (Franks et al. 2010). The most common EOD found in children with hypertension is left ventricular hypertrophy (LVH) (Daniels 1999 ; Daniels et al. 1998a; McNiece et al. 2007a; NHBPEP 2004; Toprak et al. 2008).

Twenty-five years ago, Burke showed an association between SBP, BSA, and left ventricular (LV) size among subjects 7–22 years old. The study did not uncover racial differences in cardiac anatomy (Burke et al. 1987). Schieken followed twin adolescents and assessed LV mass, BP, height, and weight at five visits from ages 11 to 17 years. Not only did Black boys have a greater LV mass at their initial visit, but the positive correlations between LV mass and weight, SBP, and heart rate were amplified in Blacks compared to Whites (Schieken et al. 1998). In a study showing that lean body mass, fat mass, and BP all affect LV mass, Daniels found significant race and gender interactions. While lean body mass was the most important factor contributing to LV mass overall, DBP was associated with LV mass in Whites but not Blacks (Daniels et al. 1995). Dekkers studied 687 subjects between ages 7 and 27 with up to 10 repeated echocardiograms (Dekkers et al. 2002). After controlling for differences in stature, the study reported that boys and Blacks had higher LV mass than girls and Whites, respectively, and that these differences appeared by early adolescence.

Other studies have further demonstrated both ethnic and gender differences in LV mass indexed to height<sup>2.7</sup> (in order to standardize by body size). Harshfield showed that the higher nocturnal SBP in Black adolescents was also associated with greater LV mass index (Harshfield et al. 2002b).

Kapuku et al. employed a multi-visit, longitudinal study to specifically assess the ability of baseline ABPM and cardiac measures to predict future cardiovascular modeling in normotensive children aged 1–19 years with known family history of cardiovascular disease (Kapuku et al. 1999). This study found that Black youths had higher baseline LV mass index, resting SBP, and relative wall thickness that could be related to findings at subsequent visits of increased BP, LV mass, and lower midwall fractional shortening in Blacks compared to Whites. Recently, Falkner and colleagues have shown in a cohort of Black adolescents that both obesity and hypertension are significantly associated with increased LV mass index (DeLoach et al. 2012; Falkner et al. 2013). Falkner also found that moderate SBP elevations above the 75th percentile were associated with increase odds of LVH after controlling for age, sex, and obesity (Falkner et al. 2013). In a study of 45 Black and 139 non-Black children, Brady found no difference in blood pressures but increased obesity and LVH rates in Black children under age 13 compared to non-Blacks. In children over age 13, BP differences were found between the two races, though obesity and LVH rates were similar in this study (Brady et al. 2010). Though LVH is thought to be a precursor to more significant cardiovascular events, treatment to control BP in hypertensive children has been shown to regress LV mass (Kupferman et al. 2010).

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### **Racial and Ethnic Differences in Response to Therapy**

Data exist primarily in adults which indicate that some ethnic groups, Blacks primarily, might demonstrate unique responses to antihypertensive therapy compared to Whites (Wright 2005, Wright et al. 2005). Recent major public health efforts have resulted in a significant increase in the proportion of hypertensive patients who are aware of their diagnosis and who are prescribed therapy (Guo et al. 2012; Hajjar 2003; Ong et al. 2006). Despite these efforts, Blacks and Hispanics still fall far behind Whites in control of BP to adequate targets (CDC 2012). The residual hypertension in

treated patients might partially explain the worse cardiovascular outcomes in Blacks compared to other ethnic groups.

Some data suggest that due to underlying causes of primary hypertension, Blacks might respond better to diuretics than to other first-line agents often used to lower BP. The ALLHAT study demonstrated improved CV outcomes, including development of heart failure and stroke, in Blacks treated with chlorthalidone compared to amlodipine or lisinopril (Wright 2005). Specifically, improved outcomes with chlorthalidone were more pronounced for some outcomes in Blacks than in non-Blacks. There are no head-to-head comparisons of antihypertensive treatment in children of different ethnic or racial backgrounds, though Li did a meta-analysis to assess the effect of race on treatment response (Li et al. 2008). Though none of the individual studies was designed to specifically assess racial differences in BP response, the meta-analysis combined six trials of ACE inhibition. Although Whites showed BP response across all trials, Blacks failed to demonstrate a significant response. Menon further showed that Blacks receiving fosinopril required a higher dose to achieve adequate SBP control (Menon et al. 2006). Similarly, Hazan studied the BP-lowering effect of olmesartan in several cohorts of children. She found that the predominately White cohort had significantly better responses compared to the cohort of Black children (Hazan et al. 2010). While further studies to confirm these differences would be helpful, these data suggest that ACEI and ARB might not be appropriate first-line agents in hypertensive Black children and adolescents.

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### **Conclusion**

As has been shown consistently in adult populations, pediatric studies suggest that BP values are not equal across racial and ethnic groups in childhood. Blacks, and likely Hispanics too, demonstrate higher BP than their White counterparts even when controlling for obesity and advanced sexual maturation. Although the many confounding differences between racial and

ethnic groups make direct comparison of BP difficult, minority children also seem to develop earlier BP target organ damage in both the heart and kidneys. Though many newer pharmacologic agents now have pediatric labeling and indications, evidence suggests that even in childhood minorities might have differences in response to treatment with antihypertensive medications. The mechanisms of the differences are not completely clear, and further examination is ongoing into the underlying causes of racial and ethnic disparity in BP. Despite differences in BP findings across racial and ethnic groups, current NHBPEP guidelines do not take these factors into account in either the diagnosis or management of elevated BP in youths. As additional data are gathered, future guidelines might consider whether racial and ethnic differences are significant enough to warrant different approaches in minority children.

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## Cross-References

- ▶ [Epidemiology of Primary Hypertension in Children](#)
- ▶ [Heritability and Familial Aggregation of Blood Pressure](#)
- ▶ [Hypertension in Older Adolescents and Young Adults](#)
- ▶ [Hypertension in the Developing World](#)
- ▶ [Monogenic and Polygenic Contributions to Hypertension](#)
- ▶ [Obesity Hypertension: Clinical Aspects](#)
- ▶ [Perinatal Programming of Arterial Pressure](#)
- ▶ [Primary Hypertension in Children](#)

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**Abstract**

Overweight and obesity in children and adolescents are common, and they are associated with the development of numerous clinical consequences such as hypertension. This chapter will provide a review of the definitions of hypertension and prehypertension in children and adolescents and then discuss the epidemiology of obesity hypertension. After examining the complex relationship between obesity and hypertension and potential mechanisms contributing to the development of obesity hypertension, clinical approaches to the management of hypertension in the setting of obesity are discussed. The clinical management is multifaceted, as one must consider that treating obesity may in fact lead to improved blood pressure. Yet, treating obesity takes time and motivation, and while awaiting the effects of changes in lifestyle on blood pressure, use of antihypertensive medications may be indicated in some children and adolescents.

**Keywords**

Obesity • BMI • Prehypertension • Hypertension

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**Introduction**

Overweight and obesity occur with increasing frequency among children and adolescents, and they are now recognized as the most common nutritional problems in developed countries. Clinical outcomes more typical of diseases of adults are now seen at younger ages. With the increased levels of obesity, a number of complications may arise, including hypertension. Other complications

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seen in this setting include type 2 diabetes mellitus (DM), dyslipidemias, obstructive sleep apnea, left ventricular hypertrophy (LVH), and orthopedic problems. Traditionally, it was felt that secondary hypertension affected children and essential hypertension affected adults only. With the change in epidemiology, it has become ever more evident that increased levels of obesity have driven the increased rates of hypertension in children.

In this chapter, the focus on obesity hypertension will include a review of some of the epidemiologic studies that demonstrate the changes in frequency of hypertensive children and adolescents. Mechanisms that link hypertension to obesity will be reviewed, and a clinical approach to the child or adolescent with obesity-associated hypertension will be proposed as well. Prevention would seem to be an optimal strategy to stem this problem, yet that may be the most difficult task to accomplish.

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## Background and Definitions

Hypertension may be defined in different ways. Clinically it is defined as the sustained level of blood pressure (BP) that over time leads to a variety of effects on target organs such as the heart (left ventricular hypertrophy), the brain and central nervous system, and the kidneys. However, since these effects take years to develop, a statistical approach to defining hypertension in the young has been adopted, based on the normative distribution of BP in healthy children and stratified by age, gender, and stature.

As discussed in detail in the Appendix, normative data for childhood BP and the definitions of BP categories were recently updated by the American Academy of Pediatrics (Flynn et al. 2017). BP readings that fall at or above the 95th percentile for age, gender and stature on at least three occasions would classify a patient as hypertensive. Those with BP between the 90th and 95th percentile are now classified as having elevated BP (replacing the term ‘prehypertension’). Hypertension is further categorized as either Stage 1 or Stage 2 depending on how far the child’s BP is above the 95th percentile.

Presently there is no direct evidence linking the stratifications of elevated BP, Stage 1, or Stage 2 hypertension with specific outcomes in the pediatric age group. However from a diagnostic perspective, the likelihood of identifying a secondary cause is directly related to the level of BP and inversely related to the age of the child (Sinaiko 1996). Hence, it is felt that pediatric patients with Stage 2 hypertension (higher relative readings for age, gender, and stature) are more likely to have secondary forms of hypertension and that the hypertension associated with obesity is more likely to be Stage 1. However, a study by Kapur et al., reviewing a cohort of 246 patients referred to four pediatric nephrology centers involved in the Midwest Pediatric Nephrology Consortium, concluded that obesity and Stage 1 hypertension should not preclude an evaluation for secondary causes (Kapur et al. 2010).

Elevated BP is also frequently seen in overweight and obese children and adolescents, and one may consider that preventive strategies could be most likely to help these patients. Effective interventions might mitigate risk before that patient becomes overtly hypertensive. The use of ambulatory BP monitoring (ABPM) is being performed more frequently in children, and it will likely be incorporated into practice more regularly. Using ABPM methodology may allow for even better characterization of BP patterns in obese children and adolescents. Babinska et al. studied a group of 109 obese patients ranging in age from 7 to 18 years, and they found that only 24% of that group had ambulatory normotension. As they further characterized the group, 25% had ambulatory prehypertension, 3% had hypertension, and almost half (48%) were classified as having severe ambulatory hypertension. They concluded that BMI is associated with the severity of ambulatory hypertension as well as an increase in daytime BP (Babinska et al. 2012). A more recent cross-sectional study of patients between 5 and 21 years of age who had undergone a 24 h ABPM compared lean subjects (BMI 15th–85th percentile) with obese (BMI >95th percentile). They found that obese subjects were less likely to display nocturnal dipping. This is similar to what is found in adults (Macumber et al. 2016).

The term metabolic syndrome (MetS) refers to a cluster of risk factors for the development of cardiovascular disease that include alterations in serum lipid levels, insulin resistance, central obesity, impaired glucose tolerance, and hypertension. There is no consensus as to what defines MetS for children and adolescents, yet several findings are considered comorbidities in the context of obesity. There have been some modifications made in a definition of the National Cholesterol Education Program Adult Treatment Panel III criteria. These criteria when applied to children and adolescents would require at least three of the following for the diagnosis of MetS: serum triglycerides >95th percentile, high-density lipoprotein (HDL) <5th percentile, systolic BP (SBP) or diastolic BP (DBP) >95th percentile, and impaired glucose tolerance defined by assessment of fasting glucose levels. For further discussion of hypertension in the MetS, please see ► [Chap. 22, “Hypertension in Children with Type 2 Diabetes or the Metabolic Syndrome”](#) by Kim et al.

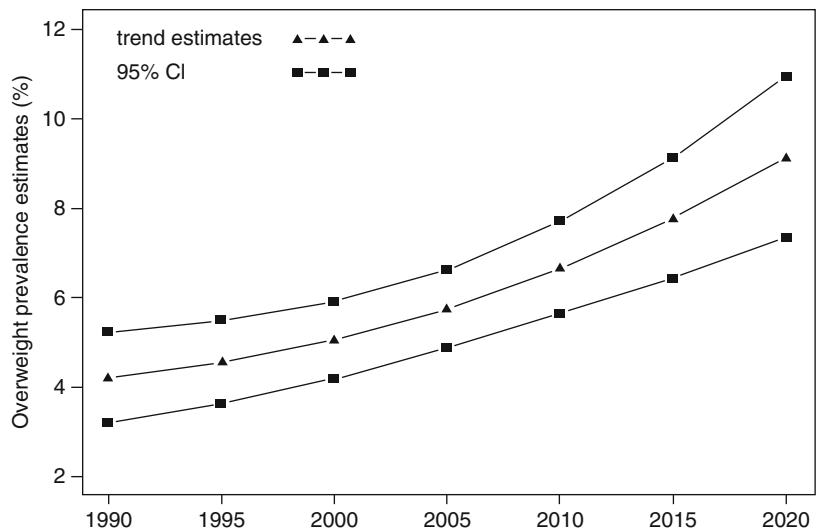
status and obesity have been increasing. Globally, obesity has reached epidemic proportions, and by 2008, it has been estimated that 40 million children less than 5 years of age are overweight (Nguyen and Lau 2012) (see Fig. 1).

Among physicians taking care of children and adolescents with elevated BP, there is a distinct impression that the link between obesity and BP has led to more children being identified with high BP and diagnosed with HTN, and yet the epidemiologic data are somewhat conflicting (Roberts and Maurer 1977; Rowland and Roberts 1982; Drizd et al. 1986; Burt et al. 1993; Luepker et al. 1988; Department of Health 2002; Shaw et al. 2000; Sjol et al. 1998; Heinemann et al. 1995). There is little direct evidence that BP has increased in the past few decades despite this concomitant epidemic of obesity, but it may just be too early to tell. A systematic review by Cholero and colleagues that included 18 studies with over two million participants studied between 1963 and 2012 showed that secular trends in blood pressure do not mirror the trends observed in overweight. A definite conclusion is difficult for a number of reasons, including the fact that the studies assessing the epidemiology of weight trends have not been the same studies assessing BP trends. There is not only a lack of standardized methodology in these studies for assessing BP in children but also a lack of a

## Epidemiology

Surveys reviewing large groups of children from the middle of the twentieth century forward have shown clearly that the prevalence of overweight

**Fig. 1** Global prevalence and trends of overweight and obesity among preschool children (Used with permission of Dr. do Onis)



consistent definition of elevated BP in children across these studies.

In addition to the changes in prevalence, an alarming rate of progression and tracking of elevated BP from childhood into adulthood is noted. Falkner reports a rate of progression from prehypertension to hypertension of 7% per year, and in that study, initial BMI and changes in BMI over time had a significant effect on BP (Falkner et al. 2008). Additionally, Redwine and colleagues noted the increased risk for developing hypertension during adolescence, with a rate of 1.1% per year (Redwine et al. 2012). In a systematic review and meta-regression analysis, Chen and Wang showed that the evidence of BP tracking from childhood to adulthood is strong and that early intervention to reduce future cardiovascular risk is important (Chen and Wang 2008). A review of the NHANES survey data examined trends in the prevalence of selected risk factors for cardiovascular disease, including hypertension, within categories of overweight/obesity. The NHANES is a cross-sectional stratified, multistage probability sample survey of the US civilian, non-institutionalized population. In the survey done between 1999 and 2008, over 3000 participants were aged 12–19 years. In that sample, there was a prevalence of 14% for prehypertension/hypertension (May et al. 2012).

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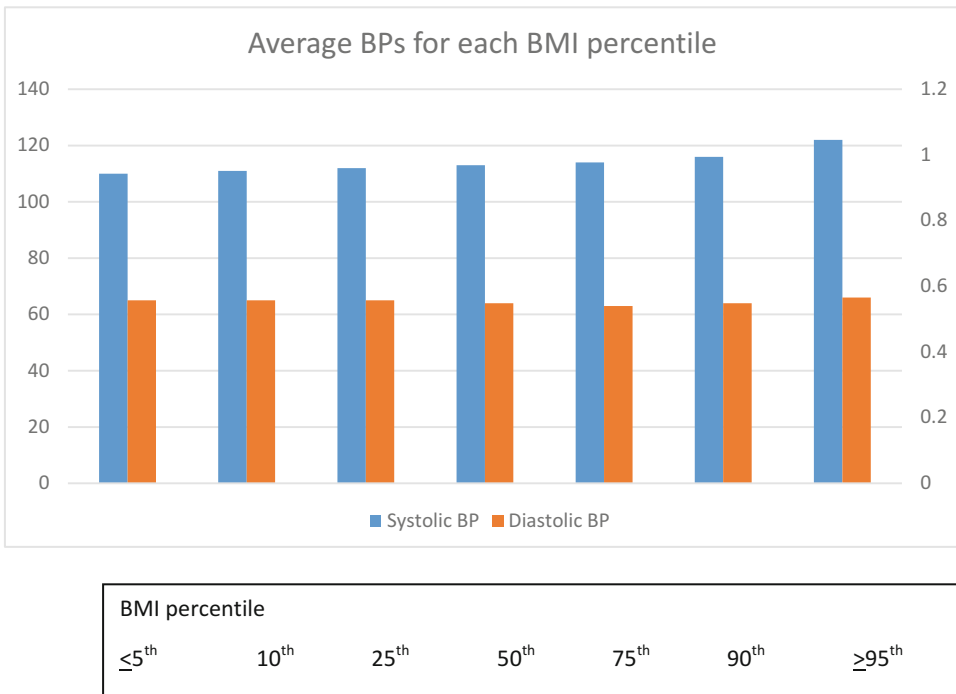
## Relationship Between Obesity and Hypertension

Several studies conducted over the past two decades have examined the association between obesity and hypertension. These have been conducted in a variety of racial and ethnic groups, and they have shown that higher BPs and/or higher prevalence of hypertension are found in children that are obese, compared with those that are lean (Elcarte et al. 1995; Verma et al. 1994; Macedo et al. 1997; Guillaume et al. 1996; Freedman et al. 1999; Sorof et al. 2002). A comprehensive study by Rosner et al. pooled data from eight large American epidemiological studies that included over 47,000 children.

It described BP differences between black and white children relative to body size, and the risk of elevated BP was significantly higher in children in the upper compared to the lower deciles of BMI, irrespective of race, gender, and age. They did find an interaction between ethnic group and BMI, such that at lower levels of BMI, blacks have higher BP and more hypertension than whites, but at the highest BMI levels, white have more hypertension than do blacks (Rosner et al. 2000).

While obesity is a very important predictor of hypertension for a patient at any age, it is also crucial to remember that the risk for hypertension and related cardiovascular factors is multidimensional. The Cardiovascular Risk in Young Finns Study, a longitudinal study of over 2000 individuals followed for 21–27 years, found that the independent childhood risk factors for adult hypertension were the individual's own systolic and diastolic BP values, parental hypertension, childhood overweight/obesity, low parental occupational status, and a high genetic risk score. This study underscores that there is a need for a multidimensional approach to caring for patients with this condition (Juhola et al. 2012).

It does appear that the early clinical course of obesity-associated hypertension can be characterized by a preponderance of systolic hypertension without diastolic hypertension. In a large school-based screening program in the Houston area by Sorof et al., the prevalence of isolated systolic hypertension was 50% as compared to 30% in non-obese subjects (Sorof et al. 2004). While it seems simple to classify a patient by weight status as “obese” or “non-obese” in determining the risk of hypertension, it is important to note that there is no threshold effect but rather the risk of hypertension in children increases across the spectrum of BMI values. Rosner et al. found a linear increase in the prevalence of diastolic hypertension in children of all race, gender, and age combinations with BMI increases across the normal range, and Sorof et al. found increasing prevalence of systolic hypertension as BMI increased from the 5th percentile to the 95th



**Fig. 2** Average systolic BP and diastolic BP at first screening for each BMI percentile category. Mean for each BMI percentile category is shown (Adapted from Sorof et al. 2004)

percentile (see Fig. 2). It is also important to realize that BP is a continuous variable that is positively associated with cardiovascular risk across the entire range of BP values. It has been observed that children with high normal BP during adolescence have a higher tendency to develop hypertension as adults (Bao et al. 1995). So, it seems quite clear that over the past four to five decades that overweight status and obesity are more common and with that comes substantial additional cardiovascular risk.

Chandramohan et al. recently reported on an interesting finding in obese children in the NHANES cohort from 1988 to 1994 (Chandramohan et al. 2012). In a retrospective analysis of 4667 children ages 6–17 years, comprised of 51% boys, 74% whites, 16% blacks, and 10% Hispanics, 12% were obese, 26% had a high waist circumference (WC), 26% had a wide pulse pressure (PP), and 9% had high BP. Prevalence of wide PP was high among obese children. A

significantly higher mean PP was observed in boys, blacks, obese, those with high WC and high BP. The adjusted odds ratio (OR) for wide PP was higher in boys, blacks, and those with high WC. These findings warrant further study to understand the potential impact of PP as a cardiovascular risk factor in all children and especially in obese children.

One must also keep in mind that there are no normative standards for BP that account for weight or BMI in children, and overweight status and elevated BP combine synergistically to increase cardiovascular risk. Adjusting BP norms in the setting of overweight status would inappropriately control for the pathologic influence of the weight effect on BP (Nguyen and Lau 2012). In order to address this issue, Rosner et al. reanalyzed the currently used pediatric normative BP values, restricting the normative population to include only the children with normal weight. Unsurprisingly, the BP levels that they

reported are slightly lower than those published in the Fourth Report (Rosner et al. 2008).

Accurately measuring BP in children is also a challenge. A key element of BP determination is having appropriately sized cuff, as a cuff that is too small may provide a falsely elevated reading. It is important to find a cuff that has appropriate length and width for the obese younger patient. The most important factor for measuring BP in the young obese patient is choosing the correct cuff-width:arm-circumference ratio. An appropriate size cuff should have a bladder width that is about 40% of the arm circumference, midway between the olecranon and acromion processes (Whincup et al. 1989; Gomez-Marin et al. 1992; Prineas 1991). The influence of the childhood obesity epidemic on BP measurement is reflected in a study by Prineas et al. They compared two cohorts of children aged 7–17 years using data from the National Health and Nutrition Examination Survey III (1998–1994) and the National Health and Nutrition Examination Survey 1999–2004. Over 5000 children were in the first cohort, and almost 8000 were in the second. They found statistically significant increases in mid-arm circumference across the two surveys, and there were increased numbers of children needing large adult BP cuffs to obtain accurate BP measurements. Given that the mid-arm circumferences of children are increasing, they concluded that there would be implications for accuracy of BP measurement (Prineas et al. 2007).

Lo and colleagues recently published data about the prevalence of both prehypertension and hypertension among children receiving primary care in community-based practices. Interestingly in that cohort of nearly 200,000 children that was diverse in age and ethnicity and that was followed in a community practice, they reported that at an index visit about 82% were normotensive, 12.7% were prehypertensive, and 5.4% had a BP in the hypertensive range. Of the children with index BP level in the hypertensive range, with follow-up BP measurement, 3.8% of them had confirmed hypertension (with an estimated 0.3% prevalence). Increasing age and BMI were both associated with both prehypertension and confirmed hypertension, and among the racial and

ethnic groups, blacks and Asians had the highest prevalence of both. The authors speculated that differences between the community-based setting and the school-based setting was a likely reason for differences in prevalence that were observed.

## Mechanisms of Hypertension in Obesity

Obesity develops as a complex interaction between genetic and environmental, as well as social, behavioral, cultural, physiological, and metabolic factors. A number of mechanisms have been studied and proposed to link obesity and hypertension, and this is an area of ongoing research. While the exact pathophysiologic mechanisms linking obesity and hypertension are still unknown, they are likely to be, multifactorial and variable. Several mechanisms are likely called into play to intertwine the pathophysiology of obesity with that of hypertension. The various mechanisms that might interact are listed in Table 1.

Clearly there are a number of hormonal mechanisms that contribute to the end result of elevated BP. The majority of data on the pathophysiology of obesity-associated hypertension are derived from studies conducted in adults and animals, but the mechanisms have also been studied in children to a limited extent. Most studies done in children have focused on primarily three main

**Table 1** Mechanisms of hypertension in the overweight/obese patient

Renal mechanisms
Impaired pressure natriuresis
Renin-angiotensin-aldosterone system alterations
Structural changes
Hormonal mechanisms
Insulin
Leptin
Neuropeptides
NPY, hypothalamic neurotransmitter
Adiponectin
Ghrelin
Endocannabinoids
Corticosteroids
Endothelial dysfunction/vascular changes

pathophysiologic mechanisms: disturbances of autonomic dysfunction, insulin resistance, and abnormalities of vascular structure and function. In patients with obesity-associated hypertension, there is likely a combination of factors that lead to hypertension. A recent review of this subject by Kotsis and colleagues underscores the point that obesity should be considered a chronic medical condition that likely requires long-term treatment (Kotsis et al. 2010).

The association between obesity and hypertension may be partly mediated by overactivity of the sympathetic nervous system (SNS). In this state of sympathetic overactivity, there may be cardiovascular manifestations such as increased heart rate and BP variability, neurohumoral manifestations such as increased levels of plasma catecholamines, and neural manifestations such as increased peripheral sympathetic nerve traffic. Consistent with the SNS overactivity hypothesis, the Bogalusa Heart Study reported that in a biracial group of children, resting heart rate was positively correlated with BP and subcapsular skinfold thickness (Voors et al. 1982) and a hyperdynamic cardiovascular state was positively associated with several measures of obesity (Jung et al. 1995). In the Houston school-based screening for obesity and hypertension reported by Sorof, it was also noted that obese hypertensive adolescents had the highest resting heart rate and non-obese normotensive adolescents had the lowest heart rate. When the analysis was restricted to only those who were hypertensive, a higher heart rate was observed in the obese compared with non-obese adolescents (Sorof et al. 2004). Rocchini et al. found that weight loss, with or without exercise, resulted in a significant reduction in heart rate in obese adolescents (Rocchini et al. 1987).

It has also been reported that obese children have increased heart rate variability and BP variability when compared with non-obese children (Sorof et al. 2004; Riva et al. 2001). The increased heart rate variability in obese children may be due to an altered balance between parasympathetic and sympathetic activity and not due exclusively to increased sympathetic activity. Using time- and frequency-domain heart rate

variability analysis, 24-h BP and heart rate monitoring in obese normotensive children has shown an increase in heart rate and in BP associated with decreased parasympathetic heart rate control (Martini et al. 2001). Furthermore, physical training in obese children appears to alter autonomic function by reducing the ratio of sympathetic to parasympathetic activity (Gutin et al. 1997). These data suggest that autonomic function has an important mediating role in the pathogenesis of obesity hypertension in children as well as in adults.

Insulin resistance is also likely involved in the pathogenesis of obesity-related hypertension in children (see also ► [Chap. 6, “Insulin Resistance and Other Mechanisms of Obesity Hypertension”](#)). Several studies have reported positive associations between fasting insulin levels and resting BP in obese children and young adults (Nguyen and Lau 2012; Voors et al. 1981; Kanai et al. 1990; Saito et al. 1992; Pozzan et al. 1997; Chen et al. 1999; Young-Hyman et al. 2001). Nonetheless, this association does not necessarily indicate causation. Lughetti et al. (2000) studied 350 obese children who were categorized as hypertensive or normotensive. Although insulin was significantly higher in hypertensive than in normotensive children, the difference was not clinically relevant. Furthermore, insulin explained only a small amount of systolic and diastolic BP variance, which disappeared after accounting for the confounding effects of age, weight, or other anthropometric dimensions.

Weight loss in obese adolescents has also been shown to result in reductions in serum insulin levels and BP (Whincup et al. 1989; Wabitsch et al. 1994) and to render previously salt-sensitive individuals insensitive to the hypertensive effects of salt-loading (Whincup et al. 1989). Based on these data, it has been suggested that the insulin resistance associated with obesity may prevent insulin-induced glucose uptake but leaves the renal sodium retention effects of insulin relatively preserved, thereby resulting in chronic volume overload and maintenance of BP elevation. However, Csabi et al. (1996) found no relationship between insulin levels and reduced sodium excretion in obese children. Thus, a causal role of

insulin resistance in the pathogenesis of obesity hypertension remains uncertain.

Altered vascular structure and function may also contribute to the pathogenesis of obesity hypertension. Ultrasound of the carotid artery has demonstrated increased intimal-medial thickness in diabetic children (Peppas-Patrikiou et al. 1998; Jarvisalo et al. 2002) and children with familial hypercholesterolemia (Tonstad et al. 1996; Jarvisalo et al. 2001; Virkola et al. 1997) compared with normal controls. In addition, decreased vascular compliance has been reported in diabetic children (Parikh et al. 2000) and children with familial hypercholesterolemia (Aggoun et al. 2000). Similar vasculopathy has been found in obese children, in whom less severe metabolic disturbances such as glucose intolerance and dyslipidemia are common. Tounian et al. (2001) reported reduced arterial compliance, lower distensibility, and lower endothelium-dependent and endothelium-independent function in severely obese compared with control children. Similarly, Rocchini et al. demonstrated decreased maximal forearm blood flow and increased minimum forearm vascular resistance in obese adolescents (Rocchini et al. 1992), which was improved after weight loss (Rocchini et al. 1988).

Insulin resistance and hyperinsulinemia are activators of the renal SNS, causing vasoconstriction and reduced renal blood flow. The reduced renal blood flow then becomes a trigger for the release of renin. With the release of renin and subsequent activation of the renin-angiotensin-aldosterone system (RAAS), there is salt and water retention which leads to BP elevation. Additionally, accumulation of perinephric fat contributes to reduced renal blood flow by compression of the renal parenchyma. This can also contribute to sodium reabsorption and higher BP. This can occur in the absence of renal scarring or chronic kidney disease (CKD).

An important adipose tissue-derived hormone that has been implicated in the development of obesity hypertension is leptin. Higher levels of leptin are associated with elevated BP and that relationship is mediated by BMI and effects on the SNS (Grontved et al. 2011). Obese individuals have also been shown to produce less adiponectin,

which is an anti-atherogenic, cardioprotective hormone that is secreted by adipocytes. Levels of this hormone are inversely correlated with BP in obese children and adolescents (Shatat et al. 2009). Vascular endothelial dysfunction occurs in the setting of obesity related to the production of proinflammatory cytokines and oxidative stress. These mechanisms impair local vasodilatory responses and increase peripheral resistance.

Many children and adolescents with obesity have sleep-disordered breathing such as sleep apnea, and they are also at higher risk for developing hypertension, especially at night (see ► Chap. 31, “Obstructive Sleep Apnea and Hypertension”). Multiple other mechanisms may occur via sympathetic activation and can contribute to higher BP, including the proinflammatory state created by cytokines such as IL-6, resulting in an acute phase response. The SNS also plays a role in energy balance and the metabolic syndrome. Fasting suppresses and meal ingestion induces sympathetic activity (Mohamed-Ali et al. 2000). Weight loss can reduce sympathetic overactivity in obese patients and that may partially explain the lower BP noted in response to dieting (Jung et al. 1979). Central fat distribution is associated with disturbances in the hypothalamic-pituitary-adrenal axis, and its disruption may be implicated in the development of the metabolic syndrome (Chrousos 1995).

Although these data have provided insights into the potential mechanisms of obesity hypertension in children, truly mechanistic studies to elucidate the pathophysiology of the early stages of the disease process have yet to be performed. To some extent, the vulnerability of the pediatric population from a research standpoint has been a barrier to performing more invasive studies such as neurography to measure peripheral sympathetic nerve traffic or interventional studies such as hyperinsulinemic euglycemic clamping. Yet, the acuity of the problem would argue for an expanded role for mechanistic studies in children to identify therapeutic interventions that may interrupt the disease process before the establishment of potentially irreversible sequelae.

## Clinical Approach and Management

When planning treatment of hypertension in any patient, potential etiologies should be considered, as it is often most effective to manage an illness or condition by treating the underlying disorder. One of the challenges of treating hypertension associated with obesity is the number of interacting features. There are generally two general approaches to treatment. A broad area of treatment to consider is non-pharmacologic management, also known as Therapeutic Lifestyle Changes (TLC) in the Fourth Report. The other area is pharmacologic management. In the area of obesity-associated hypertension, treatment of obesity may have beneficial effects on BP, and yet direct treatment of high BP may be undertaken while efforts to treat the obesity are ongoing. Table 2 displays elements of a comprehensive treatment plan to consider. It is generally accepted that patients with elevated BP without evidence of target organ damage should initially be counseled in ways to affect therapeutic lifestyle changes. In patients with diagnosed HTN, either Stage 1 or Stage 2, lifestyle changes should at least be used as adjuncts to pharmacologic therapy.

### Lifestyle Changes: Prevention of Obesity

Ideally, prevention would be a key issue to consider, and yet several challenges remain. Healthy lifestyle choices by families that include children should reduce the incidence and therefore prevalence of many chronic conditions, and

**Table 2** Treatment considerations in the overweight/obese patient with hypertension

Non-pharmacologic elements	Pharmacologic elements
Weight loss	Medications for blood pressure lowering
Diet	
Exercise	Medications for obesity
Avoidance of tobacco	
Avoidance of alcohol	
Stress avoidance	

obesity is certainly one of the most common. Prevention of obesity is a very important public health priority. The American Academy of Pediatrics recently addressed this with a clinical report entitled “The Role of the Pediatrician in Primary Prevention of Obesity” (Daniels et al. 2015) that updated and replaced an earlier policy statement “Prevention of Pediatric Overweight and Obesity” (Krebs et al. 2003) and complements the AAP-endorsed expert committee report “Recommendations for Prevention of Childhood Obesity” (Davis et al. 2007). The report also discusses a variety of practical approaches of prevention including the identification of children at risk, the role of education, the role of theory-based techniques of behavior modification, ways to manage the food and activity environment, encouragement of self-monitoring, focusing on family-based interventions, helping parents to develop both parenting and communication skills and the techniques of motivational interviewing. Practice-based skills are discussed, and issues of actual and activity targets are delineated. Very specific guidance about developmental stages is given as well, as the approach to prevention in early infancy is quite different from that in older children and adolescents.

### Lifestyle Changes: Weight Loss, Diet, and Exercise

All clinical practice guidelines on childhood hypertension endorse weight loss, diet, and exercise as potential lifestyle changes that may be beneficial in the treatment of HTN. If obesity is a cause or at least the primary contributor to HTN for the child, then one must tackle obesity as the underlying problem. Since weight loss, involvement in aerobic exercise, and modifications of the diet have been shown to reduce BP in children and adolescents, it also seems reasonable to believe that these approaches should be considered the primary treatment of hypertension when the hypertension is related to obesity.

While dietary advice is recommended as first line therapy, there really is limited evidence that it works. However within the spectrum of



therapeutic lifestyle changes (non-pharmacologic management strategies), dietary interventions have been studied most often. One must keep in mind that dietary interventions may include not only adjustments to caloric intake but also adjustments to the nutritional components of the diet.

A number of nutrients have been examined such as sodium, potassium, calcium, folate, and caffeine, and sodium has probably been the most extensively studied. While not every individual will be salt-sensitive, modest sodium reduction would be beneficial, given the typical diet of most children and adolescents in the United States. Yang and colleagues reviewed NHANES data on over 6000 children and adolescents and discovered that sodium intake was positively associated with systolic BP and risk for prehypertension and hypertension and that association appeared to be stronger among those who were overweight and obese (Yang et al. 2012).

Looking first at weight loss in general, there have been both observational and interventional studies showing beneficial effects of weight loss in pediatric patients, yet there have been limited controlled trials. One of the first such studies by Brownell et al. (1983) reported BP reductions of up to 16/9 mmHg in obese children who achieved significant weight reduction after 16 months of dietary counseling. In a retrospective study based on a 10-year period of observation, Clarke et al. (1986) reported that children whose ponderosity increased over that period had a relative increase in BP by 18 percentiles compared with their peers, whereas children whose ponderosity decreased had a relative reduction in BP by 13 percentiles.

Rocchini and colleagues conducted a randomized, controlled trial over a 20 week period, and three interventions were studied: diet alone, diet along with exercise, and a control group with no intervention at all. Changes in systolic BP from baseline in the diet plus exercise group, diet alone group, and control group were  $-16$  mmHg,  $-10$  mmHg, and  $+4$  mmHg, respectively. This study provides the most definitive evidence that weight loss, particularly in conjunction with exercise, can be beneficial in the management of obesity hypertension in children. However, the

long-term benefits of weight loss on BP remain to be defined because it is unknown whether the decline of BP observed during acute weight loss can be maintained (Rocchini et al. 1988).

Figuroa-Colon et al. (1993) found that BP was significantly reduced compared with baseline at all points of a study comparing two hypocaloric dietary modifications in obese children. Wabitsch et al. reported a BP reduction of 9/5 mmHg associated with a weight reduction of 8.5 kg after a 6-week dietary intervention in obese adolescent girls (Wabitsch et al. 1994). Similarly, Gallistl et al. reported an 8/7 mmHg BP reduction associated with weight loss of 3.9 kg after a 3-week diet and exercise program in obese children (Gallistl et al. 2001).

Weight loss not only reduces BP but it may also improve some of the other cardiovascular risk factors that cluster with obesity, such as dyslipidemia and insulin resistance. While this is a benefit to the patient and it makes sense, losing weight is generally a challenge for most patients.

Beyond weight loss in general, next one must also consider components of the diet in the control of BP. When looking more specifically at children with HTN, one can see that a few studies have looked at components of diet as modifiable elements of a child's life that can result in improvement. In a 2-year trial of potassium and calcium dietary supplementation in Chinese children who had salt-sensitive hypertension, improvement in systolic BP was observed (Mu et al. 2005). Moore et al. looked at a group of children enrolled in the Framingham Heart Study, and they showed some beneficial effects on BP of a diet rich in fruits, vegetables, and dairy products (Moore et al. 2005).

Dietary Approaches to Stop Hypertension, also known as the DASH diet, has been proven to lower BP primarily in adults and also in children and adolescents. The DASH diet goes beyond a low-sodium diet and provides guidance for a diet rich in fruits and vegetables as well as low-fat or non-fat dairy products. This diet is one that is low in sodium and enriched with potassium and calcium, and it also incorporates a higher intake of micronutrients such as folate and measures to reduce dietary fat intake. The reduction in dietary fat intake is important, given the likelihood for diets

higher in fat content to promote weight gain as well as alterations in lipid levels (Appel et al. 1997).

Couch and colleagues performed a study that compared an intensive 3-month intervention to a more routine type of nutritional intervention in adolescents referred to a tertiary care center hypertension clinic and diagnosed with either prehypertension or hypertension. Two groups of children were studied over a 3-month period. One group was received the DASH intervention, which consisted of extensive counseling as well as very close follow-up. This included a 1 h face-to-face counseling session between a dietician, the subject, and parent, a manual to take from the study center, eight weekly and two bi-weekly phone calls by a trained interventionist, and four bi-weekly mailings. The routine care (RC) group received a more standard dietary intervention, with the 1 h counseling session done in the clinic setting and provision of a take-home booklet that basically discussed reduction of sodium intake, weight control by limiting high fat foods, reduction of portion size, and eating nutrient-dense forms of food. From baseline to posttreatment, the relative change in systolic BP among the subjects in the DASH intervention was  $-7.9\%$  as compared to  $-1.5\%$  in the RC group ( $p < 0.01$ ), but there was no significant change for diastolic BP. Other findings, while not statistically significant, did show potential for beneficial effects, such as 50% of the DASH group achieving BP normalization posttreatment compared with 36% in the RC group. By 3-month follow-up, 61% in the DASH group had normal BP, while only 44% in the RC group did ( $p = 0.36$ ). In addition to beneficial effects on BP, the DASH intervention group also had significant changes in dietary intake of fruits vegetables and dairy products (Couch et al. 2008).

A study by Gunther and colleagues in children and adolescents with diabetes mellitus and hypertension explored the associations of the DASH diet in this population. It showed that children with type 1 DM following DASH guidelines had a markedly decreased chance of having hypertension, but this was not observed in children with type 2 DM. In that study, the majority of subjects with type 2 DM were obese (Gunther et al. 2009).

Now the shift to the effects of exercise will be considered, though the evidence here is limited. The types of exercise felt to be most beneficial are aerobic activities such as running, brisk walking, swimming, or cycling, as opposed to static forms of exercise such as weight-lifting. Some children may be participating in group activities in school physical education classes or in team sports, but they may need to increase the intensity of their involvement of the frequency at which they do these activities. While increasing these activities, attention should also be paid to reducing the amount of screen time a child has, such as time in front of a television or computer. Clearly, these interventions are the safest and least prone to having side effects or adverse effects, yet they remain challenging for families to pursue, and there is minimal evidence as well that these interventions are efficacious.

While exercise training has also been shown to reduce BP for a limited period of time, typically on the order of 3–6 months, once the exercise ends, it seems that BP returns to pretreatment levels (Alpert 2000; Ribeiro et al. 2005).

It is also important to consider giving children and families some concrete recommendations, rather than providing the general advice to “increase activity.” Torrance and colleagues would suggest that children do 40 min of moderate to vigorous aerobic exercise 3–5 days per week (Torrance et al. 2007). This could be a goal to achieve, yet it would certainly require a high degree of motivation on the part of not only the patient but also the patient’s family.

A couple of recent key reviews to consider now that a number of studies in this area have been conducted are meta-analyses that focus on these lifestyle interventions. Aburto et al. assessed the effects of decreased sodium intake on not only BP but also a number of other elements leading to cardiovascular risk. The review was done in both adults and children, but to focus on the children here, they reviewed nine controlled trials and one cohort study in children. In assessing the data analyzed, the authors felt that moderate quality evidence in children showed that a reduction in sodium intake reduced BP. They concluded that the totality of evidence suggested that most people

would likely benefit from reduction in sodium intake (Aburto et al. 2013). Ho et al. looked more broadly at the effects of lifestyle interventions on cardio-metabolic outcomes in overweight children. That review of English-language articles published between 1975 and 2010 included 38 eligible studies, and 33 of them had complete data for meta-analysis on weight change. Fifteen of them reported on lipid values, fasting insulin levels or BP.

Looking specifically at the studies that focused on BP, nine compared lifestyle intervention with no-treatment or wait-list control, seven compared lifestyle intervention with usual care, and two compared lifestyle intervention compared with written educational materials only. Of these 18 studies, 10 showed a statistically significant improvement in systolic and/or diastolic BP as an outcome.

The authors concluded that lifestyle interventions could lead to improvements in both weight and various cardio-metabolic outcomes and that further research is needed to determine optimal length, intensity, and long-term effectiveness of these interventions (Ho et al. 2012).

There are clearly beneficial effects to therapeutic lifestyle changes, and it seems that the evidence available supports a treatment strategy that would include elements of weight loss that not only limit caloric intake but also recommend certain components of a healthy eating plan, while also encouraging physical activity. Especially in the asymptomatic patient, these treatment recommendations can be made right away, knowing that any of these changes will take some time to take effect.

### **Lifestyle Changes: Other Elements to Consider**

While there may be no data in children and adolescents regarding avoidance of tobacco, alcohol, and stress on BP control, it seems prudent to counsel pediatric and adolescent patients about these practices.

While it will take some time for results to be available, there is a study underway to implement

guidelines that aim to reduce the risk of eventual cardiovascular disease. The Young Hearts, Strong Starts study is a cluster-randomized trial that targets BMI, blood pressure, and tobacco use. It will test strategies to facilitate the adoption of the National Heart, Blood, and Lung Institute's Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. It is designed to compare baseline measures of BMI, BP, and tobacco using two different strategies. One of them is a multifaceted, practice-directed intervention, and the other is standard dissemination of the guidelines. A detailed description of the project can be found in the reference (LaBresh et al. 2014).

### **Management of Obesity**

Most interventions for pediatric obesity have focused on behavioral approaches to diet and physical activity to address the main components of energy balance. Although these approaches have been shown to have both short- and long-term beneficial effects on BMI in selected patients (Epstein et al. 1990), such success has not been uniform. This management approach is very labor intensive and is often not covered by medical insurance (Tershakovec et al. 1999). Other dietary approaches which have been tried include the very-low-calorie diet (National Institutes of Health 1993) and the protein-modified fast (Bistrian 1978). Although these dietary approaches can be effective in selected patients, they have also been associated with important adverse effects. The AAP Clinical Report referenced above (Daniels et al. 2015) lays out a number of practical strategies that can be employed in confronting obesity.

Surgical approaches have been used in morbidly obese adolescents, and while clearly not appropriate for a large number of patients, over the past two decades, bariatric surgery volumes have increased. In fact, the volumes have doubled from about 800 cases in 2003 to 1600 procedures in 2009. Important questions about the safety and efficacy of these procedures are being studied within a prospective, multicenter, observational study called the Teen-Longitudinal Assessment

of Bariatric Surgery (Teen-LABS). A report by this group in 2016 showed outcomes of 242 adolescents who had undergone weight loss surgery at one of the five participating centers. The procedures studied were Roux-en-Y gastric bypass (161 subjects) and sleeve gastrectomy (67 participants). These subjects were studied extensively, and at 3 years after the procedure, there was a mean weight loss of 27%, remission of elevated BP in 74% of subjects, and improvement in a number of other elements of their metabolic conditions that were studied, including glucose tolerance, renal function, and lipid abnormalities. The authors concluded that there were significant improvements in weight, cardiometabolic health, and weight-related quality of life at the time point of 3 years post-procedure. While not risk-free, there were noted micronutrient deficiencies and the need for additional abdominal procedures. Clearly there are benefits noted for some patients, and more follow-up from this group will be interesting (Inge et al. 2016).

### **Pharmacologic Considerations: Anti-obesity Medications**

The role of pharmacologic management in the management of pediatric obesity has been controversial. The history of pharmacological treatment of obesity in adults is replete with problems, and there have been few well-controlled studies to show that the available drugs are well tolerated and effective for use in obese children. Many of the drug treatments that have been tried in adults have resulted in significant complications, such as those seen with amphetamines and fenfluramine/dexfenfluramine (which is now off the market due to adverse effects). This history has reinforced the debate regarding whether medications should be used to treat obesity except under the most extreme circumstances. On the one hand, obesity is a chronic problem requiring long-term management and potentially long-term exposure to the adverse effects of medications, an issue of particular concern in growing and developing children. On the other hand, evidence for the benefits of weight

loss on BP in children may tilt the risk-benefit balance in favor of a more aggressive management approach for the prevention of future cardiovascular disease.

In the United States, the Food and Drug Administration (FDA) has approved very few drugs for pharmacological therapy of obesity (Singhal et al. 2007), one of which is orlistat (sibutramine, an inhibitor of the reuptake of serotonin and norepinephrine, has been withdrawn from the US market at the request of the FDA). Orlistat is a gastrointestinal lipase inhibitor that may hold promise for safe and effective pharmacological treatment for childhood obesity. A 1-year placebo-controlled trial in which orlistat was used along with a hypo-caloric diet, exercise, and behavior therapy showed a significant decrease in BMI along obese American adolescents (Godoy-Matos et al. 2009).

Fairly recently, the Food and Drug Administration (FDA) approved the use of two new drugs as adjuncts to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m<sup>2</sup> or greater (obese), or 27 kg/m<sup>2</sup> or greater (overweight) in the presence of at least one weight-related comorbidity, such as hypertension, type 2 diabetes mellitus, or high cholesterol (dyslipidemia). Qsymia (phenteramine and topiramate extended-release) is the first FDA-approved once daily combination therapy, and it was approved for use in July 2102. Belviq (lorcaserin) is a selective agonist of the serotonin (5-hydroxytryptamine) 2C (5-HT 2C) receptor was also approved for use in 2013. Both of these drugs reduce appetite and may induce a negative energy balance. These medications have not yet been extensively studied in children or adolescents (Colman et al. 2012).

### **Pharmacologic Considerations: Antihypertensive Medications**

Pharmacologic therapy of hypertension in the setting of obesity needs to be considered as well. It is important to think of medication as adjunctive therapy while continuing to encourage the

attempts at weight reduction and other approaches discussed above. Depending upon when the child is noted to have hypertension, continued linear growth can have a favorable effect on BP, and if the rate of rise in height outpaces the rate of rise in weight, it is not only possible for the child to “outgrow” the need for medication to control BP but also therapy may be stepped down over time. Compelling indications for initiating pharmacotherapy include symptomatic hypertension, secondary hypertension with identified specific causes, evidence of target organ damage such as left ventricular hypertrophy (LVH) on echocardiography.

All pharmacologic agents provide potential benefits for treating elevated BP, and yet every medication has the potential for side effects, and in the setting of obesity, there is a need to consider some of the potential drawbacks of certain classes of antihypertensives. Detailed reviews of the classes of antihypertensive medications can be found elsewhere, but it is important to consider the potential benefits and drawbacks of these classes in the context of obesity.

Diuretics serve to decrease intravascular volume and cardiac output, and yet they may also increase SNS and RAAS activity. They also may have dose-related worsening of insulin-resistance and dyslipidemia, which can be concerning in patients with obesity. Beta-blockers antagonize the enhanced SNS activity of obesity-related hypertension, and yet they may also increase the risk of weight gain and diabetes, and they may contribute to interference with carbohydrate and lipid metabolism. These classes of agents may need to be used judiciously in obese hypertensives because of these potential adverse effects.

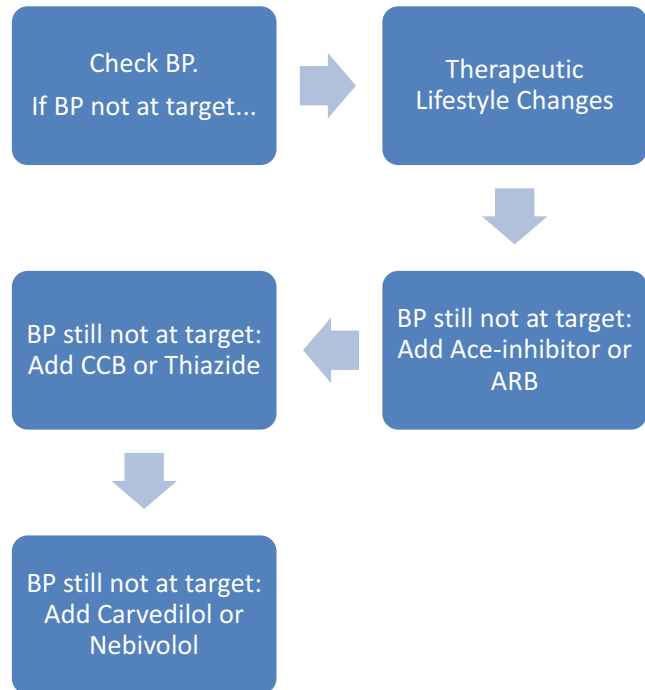
Calcium-channel blockers offer advantages of decreased peripheral vascular resistance and intravascular volume, with no excess risk of diabetes, but a potential drawback is neuroendocrine activation. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) offer a number of advantages for obese patients, as they decrease peripheral vascular resistance without excess risk of inducing diabetes, with no dyslipidemic effects, and potential for regression of left ventricular hypertrophy (LVH).

Alpha-blockers are felt to be safe and effective, with some advantages for patients with dyslipidemia and glucose intolerance, but there are limited data in not only obese patients but also children and adolescents. Centrally acting agents are known to decrease SNS activity, but they may also impair glucose tolerance and contribute to weight gain (Sharma et al. 2001).

There has been an evolution in the understanding of the treatment of hypertension in children and adolescents over the past decade. This has been fueled in part by the increased attention paid to the clinical problem, given the increasing numbers of children and adolescents being diagnosed with this condition. There has also been a growing number of clinical trials performed and completed that demonstrate the BP-lowering effects of antihypertensives and the side effect profiles of these medications and that has led to FDA-labeling of many antihypertensive medications for use in children and adolescents. However, none of these trials has provided definitive data on the optimal first line agent for this patient population. Many of the subjects who participated in these trials were overweight or obese, and yet there have not been trials specifically targeting the obese childhood or adolescent population with hypertension. In a recent review of antihypertensive medication use, Welch et al. showed that despite recent legislative initiatives, there are still medications without adequate pediatric labeling, and so there remains a gap between drugs that are approved, indicated, and labeled for use and the actual medication usage (Welch et al. 2012). Clinical experience and other approaches discussed here will continue to guide treatment of hypertension in younger obese patients (Batsky 2012).

In the review of hypertension associated with obesity, Kotsis and colleagues propose a general approach to treatment. Figure 3 shows an adapted version of these recommendations, although one must keep in mind that this approach has not been evaluated in the pediatric population. They do provide appropriate rationale for choices in this approach, such as ACE-inhibitors and angiotensin receptor blockers being used as first-choice agents as they are associated with lower incidence of

**Fig. 3** Hypertension associated with obesity: general set of guidelines for treatment (Adapted from Kotsis et al. 2010)



diabetes and have favorable effects on LVH and nephropathy. Calcium antagonists are also considered, as they are metabolically neutral. Thiazide diuretics at low dose may be beneficial, yet their adverse effects may limit use. While beta-blockers may impair glucose and lipid metabolism, these effects seem to be less pronounced with the new vasodilating beta-blockers like carvedilol and nebivolol (Kotsis et al. 2010).

## Conclusions

Treatment of the obese child or adolescent with hypertension requires a multidimensional approach to provide optimal care and best outcomes. Both non-pharmacologic and pharmacologic strategies will need to be employed to address issues of BP, optimal diet, exercise, and weight reduction to achieve the desired outcomes. In addition, one must recognize that this is an issue that affects not only the individual patient being treated but also the rest of that patient's family. In many ways, it is encouraging to initiate some dialogue with the family about treatment

strategies that will have collateral benefits for other members of the family. Getting siblings involved with activities that promote a healthy lifestyle can be beneficial not only for the patient, so that she does not feel "singled out," but also for the other siblings to take part in activities that do not lead to their feeling "left out." A key element to address with the family is that it takes a high degree of motivation to initiate changes and an even higher degree of motivation for these changes to take effect and persist.

## Cross-References

- ▶ [Epidemiology of Cardiovascular Disease in Children](#)
- ▶ [Epidemiology of Primary Hypertension in Children](#)
- ▶ [Hypertension in Children with Type 2 Diabetes or the Metabolic Syndrome](#)
- ▶ [Insulin Resistance and Other Mechanisms of Obesity Hypertension](#)
- ▶ [Nonpharmacologic Treatment of Pediatric Hypertension](#)

- ▶ Pharmacologic Treatment of Pediatric Hypertension
- ▶ Stress and Salt Sensitivity in Childhood Hypertension

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## Abstract

The childhood obesity epidemic has been accompanied by an increase in complications of obesity such as the metabolic syndrome and type 2 diabetes. Obese youth with the metabolic syndrome are frequently hypertensive and may present with clinically significant evidence of hypertensive target-organ damage. There are important considerations in the approach to treating hypertension in young patients with the metabolic syndrome or type 2 diabetes, which include the primacy of lifestyle approaches to effect substantial weight loss, increases in exercise, and reduced caloric and salt intake. The cardiovascular effects of oral hypoglycemic agents, and the potentially diabetogenic effects of certain antihypertensive medications must

also be considered. A comprehensive approach, including nonpharmacologic measures, the use of hypoglycemic and antihypertensive medications, and perhaps even bariatric surgery in selected patients, is indicated in order to reduce future cardiovascular risk.

## Keywords

Pediatric hypertension • Metabolic syndrome • Type 2 diabetes

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## Introduction

Of the many consequences of childhood obesity, the early development of type 2 diabetes (T2DM) is perhaps the most worrisome, given its long-term cardiovascular and renal sequelae. The metabolic syndrome (MetS), a cluster of risk factors for cardiovascular disease and T2DM with a common etiology related to insulin resistance, also has substantial adverse cardiovascular manifestations and commonly occurs in obese children and adolescents. This chapter will focus on manifestations of hypertension (HTN) in children with T2DM or MetS, with a major focus on treatment considerations, particularly as these pertain to the use of hypoglycemic and antihypertensive medications.

- Normal BP in children and adolescents is defined as systolic and diastolic BP readings below the 90th percentile for age, sex, and height.
- Hypertension is defined as systolic or diastolic BPs persistently  $\geq$ 95th percentile.
- Prehypertension is defined as BP values between the 90th and 95th percentiles, or  $\geq$ 120/80 for adolescents. (National High Blood Pressure Education Program Working Group on High Blood Pressure in C & Adolescents 2004)

There are published tables that list the normative BP values for adolescents  $\leq$ 17 years of age; these are available elsewhere in this text. For adolescents  $\geq$ 18 years of age, the adult BP classification scheme should be used. A comparison of the pediatric and adult BP classification schemes is presented in Table 1. It should be noted that as this chapter was being written, both the adult and pediatric BP guidelines were in the process of being revised. Highlights of the new pediatric BP guideline can be found in the Appendix to this text.

## Classification of Blood Pressure in the Young

Traditional cardiovascular end-points used to define levels of HTN in adults such as myocardial infarction and stroke rarely occur during childhood and adolescence. Therefore, the definition of HTN in the young is statistical, derived from analysis of a large database of blood pressure (BP) readings maintained by the National High Blood Pressure Education Program (NHBPEP). These readings were obtained in healthy children and adolescents in a variety of screening studies such as the National Health and Nutrition Examination Survey (NHANES).

## Hypertension in the Metabolic Syndrome

The Metabolic syndrome (MetS) is a constellation of metabolic factors associated with the risk of developing atherosclerotic cardiovascular disease

**Table 1** Classification of hypertension in children, adolescents, and adults

Blood pressure classification	Children and adolescents $\leq$ 17 years of age	Older adolescents ( $\geq$ 18 years of age) and adults
Normal	SBP and DBP <90th percentile; or <120/80 in adolescents $\geq$ 13 years old	SBP <120 mmHg and DBP <80 mmHg
Elevated BP	SBP or DBP 90–95th percentile; or 120–129/<80 mmHg for adolescents $\leq$ 13 years old <90th percentile	SBP 120–129 mmHg and DBP <80 mmHg
Stage 1 hypertension	SBP or DBP >95th percentile up to the 95th percentile +11 mmHg; or BP 130–139/80–89 mmHg for adolescents $\geq$ 13 years of age	SBP 130–139 mmHg or DBP 80–89 mmHg
Stage 2 hypertension	SBP or DBP $\geq$ 95th percentile +12 mmHg for age, sex, and height; or >140/90 mmHg for adolescents $\geq$ 13 years of age	SBP 140–159 mmHg or DBP 90–99 mmHg

*DBP* diastolic blood pressure, *SBP* systolic blood pressure  
Adapted from Flynn et al. (2017)

and diabetes mellitus and includes central obesity, dyslipidemia, abnormal glucose metabolism, and elevated BP. The individual risk factors that make up MetS are therapeutic targets for lifestyle modification, medications, and surgical interventions (Beltran-Sanchez et al. 2013; Eckel et al. 2010).

The overall prevalence of MetS in adults has been reported in North America as 21.8%, increasing with age – 6.7% for those 20–29 years old, and 43.5% for 60–69 years old and 42% for ≥70 years old (Ford et al. 2002). Prevalence and trends of MetS in adult US population from 1999 to 2010 were analyzed using data from NHANES (Beltran-Sanchez et al. 2013). From 1999 and 2000 to 2009 and 2010, the prevalence of MetS decreased from 25.2% to 22.9%, and the prevalence of hypertriglyceridemia and HTN decreased (Beltran-Sanchez et al. 2013). Decreases in hypertriglyceridemia, suboptimal high density lipoprotein, and HTN were correlated with increases in the use of antihypertensive and lipid-modifying medications (Beltran-Sanchez et al. 2013).

Rates of HTN among US children and adolescents from 1999 to 2012 have recently been examined using data from NHANES (TODAY Study group 2013). In 2011–2012, slightly more than 1 in 10 children and adolescents aged 8–17 years had either prehypertension or high blood pressure (Kit et al. 2015). There was no change from 1999–2000 to 2011–2012 in borderline BP (7.6 versus 9.4%) or high BP (10.6 versus 11.0%) (Kit et al. 2015). The reasons for these trends require further investigation (Kit et al. 2015).

While it is clear that components of the MetS also can be identified in children and adolescents, there is no consensus definition for the MetS for the pediatric population. Applying modified National Cholesterol Education Program (NCEP) or Adult Treatment Panel III (ATP III) criteria to children and adolescents, three or more of the following constitute the MetS: serum triglycerides (TG) >95th percentile, HDL cholesterol <5th percentile, systolic or diastolic blood pressure (BP) >95th percentile, and impaired glucose tolerance (Weiss et al. 2004). Using these modified criteria, Weiss et al. found that 39% of those who were moderately obese and 50% of those who were severely obese had the MetS

and the prevalence increased with increasing degrees of insulin resistance when adjusting for race and degree of obesity (Weiss et al. 2004). Using more stringent criteria, Cook et al. reported that the prevalence of MetS in the NHANES III cohort was 29% in obese participants (BMI ≥95th percentile), 6.8% in overweight participants (BMI 85th–95th percentiles), and 0.1% in normal weight participants (BMI <85th percentile) (Cook et al. 2003). Importantly, the criteria utilized by Cook et al. to define the MetS included BP ≥90th percentile, a lower level than in the analysis of Weiss et al.

The International Diabetes Federation (IDF) Task Force on Epidemiology and Prevention of Diabetes proposed a consensus definition for the MetS in childhood that utilizes age-based criteria (Table 2) (Zimmet et al. 2007a, b). Obesity is a central, essential component of their definition, with other comorbidities such as HTN following. Waist circumference has been shown to be an independent predictor of insulin resistance, lipid levels, and blood pressure (Lee et al. 2006). It is important to note that the IDF chose to compensate for variation in child development

**Table 2** Proposed IDF\* Definition of metabolic syndrome in children and adolescents

Age 6 to <10 years	Obesity ≥90th percentile as assessed by waist circumference Metabolic syndrome cannot be diagnosed, but further measurements should be made if family history of metabolic syndrome, type 2 diabetes mellitus, dyslipidemia, cardiovascular disease, hypertension, or obesity
Age 10 to <16 years	Obesity ≥90th percentile (or adult cutoff if lower) as assessed by waist circumference Triglycerides ≥1.7 mmol/L HDL-cholesterol <1.03 mmol/L Blood pressure ≥130 mmHg systolic or ≥85 mmHg diastolic Glucose ≥5.6 mmol/L (oral glucose tolerance test recommended) or known type 2 diabetes mellitus
Age >16 years	Use existing IDF criteria for adults

\*Abbreviations: *IDF* International Diabetes Federation, *MS* metabolic syndrome  
Lee et al. 2006 and Steinberger et al. 2009

and ethnicity, age-related changes in waist circumference, and other factors by not defining the specifics of the MetS in children under 10 years of age beyond obesity, implying that the diagnosis of MetS not specifically be made in younger children. In the 10–16 year-old group an absolute BP level was chosen, reflective of the adult MetS criteria with the same cutoff points used for systolic and diastolic HTN, rather than a BP percentile to denote elevated BP. This IDF definition of the pediatric MetS will require validation in large-scale studies (Steinberger et al. 2009) and should best be considered as a starting point that may be changed as further data and information emerge. Recent data have been interpreted to suggest that further development of the MetS criteria is indicated for children in the prepubertal age range; for example, in one recent study from Europe features including dyslipidemia and HTN were similarly prevalent in prepubertal as compared to pubertal and postpubertal obese children (Steinberger et al. 2009; Olza et al. 2011).

Further challenges exist, as the MetS as a diagnosis in a particular child may change, likely related to the dynamic state of physiological changes during puberty. For example, the known changes in insulin sensitivity seen in normal puberty, with a physiological decrease in insulin sensitivity during mid-puberty mirrored by a compensatory rise in insulin secretion. The diagnosis of MetS, as defined by various groups, including IDF and AHA, has appeared to be inconstant in more than half of adolescents in a prospective cohort of 1098 children – over half diagnosed as having MetS at baseline no longer fulfilled the criteria on follow-up over 3 years (Goodman et al. 2007). Understandably, in that cohort, a new diagnosis of MetS in other participants was made over the same follow-up period. Thus, there is not a stable picture of what constitutes the MetS in adolescents.

Other reasons for difficulties in defining MetS problematic include methodological and physiological limitations. Normal lipid levels vary with age, sex, and race (Beltran-Sanchez et al. 2013). Obtaining fasting blood samples would likely make the diagnosis and detection simple and cheap. However, blood sample obtained after a

glucose load is a better marker of insulin resistance than a fasting sample (Beltran-Sanchez et al. 2013). Another obstacle includes the lack of standardized central obesity measures in children (Beltran-Sanchez et al. 2013).

Lipid partitioning, i.e., the distribution of fat in the body, is a major element of insulin sensitivity and is strongly related to other metabolic biomarkers such as systemic inflammation. Lipid partitioning is closely more related to the metabolic phenotype of obese children and adolescents than the degree of obesity. Further, children of different ethnic backgrounds vary in their patterns of lipid partitioning, the major contributor to insulin resistance, and also vary in their metabolic profiles (Liska et al. 2007). African American youth seem to be relatively “protected” from the development of metabolic syndrome. However, African American adults are known to have overall worse cardiovascular outcomes than other groups (Beltran-Sanchez et al. 2013). Lastly, body mass index (BMI) is used to define overweight and obese categories. Obesity per se does not automatically indicate the presence of metabolic syndrome.

Ultimately, whether the use of the MetS construct stands up to the true definition of a “syndrome,” or not, is in our opinion of secondary importance to the primacy of its clinical usefulness to identify a pattern of increased cardiovascular risk seen broadly across the obese population. In other words, the concept has clinical utility as a framework for the development of an intervention plan for the individual patient.

Given that elevated BP is one of the criteria for diagnosis of the MetS, it follows that the majority of persons with the MetS exhibit some degree of BP elevation. For example, HTN is strongly associated with fasting hyperinsulinemia (Sinaiko et al. 1997), and with the cluster of dyslipidemia, insulin resistance, and obesity in children aged 11–15 years (Sinaiko et al. 2002). However, the association between HTN and individual components of the MetS in children may be less strong. Longitudinal studies do show, though, that elevated systolic BP in childhood strongly predicts the development of adult MetS (Sun et al. 2007). The MetS has been identified as

a strong independent predictor of cardiovascular events in hypertensive persons, amplifying the cardiovascular risk associated with HTN (Schillaci et al. 2004). The process of atherosclerosis starts at an early age and is already linked to obesity and other components of the MetS in childhood (Berenson et al. 1998). Accurate identification and appropriate treatment of children and adolescents with the MetS is thus critical for prevention of future cardiovascular disease.

### **Surrogate Markers for Early Cardiovascular Disease**

Intima-media thickness (IMT) is an early marker of cardiovascular disease in childhood and is a surrogate marker for early atherogenesis (Beltran-Sanchez et al. 2013). Only the most conservative definitions of metabolic syndrome were significantly correlated with degree of IMT (Reinehr et al. 2008). The presence of impaired glucose tolerance had a high predictive positive value for the top quartile of IMT (Reinehr et al. 2008). The presence of impaired glucose tolerance was interpreted as a pro-atherogenic metabolic state (Eckel et al. 2010). Some investigators suggest that actual carotid plaques rather than IMT are true marker of atherosclerosis in children. Carotid plaques have not been sufficiently studied to be deemed an outcome variable in children.

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### **Hypertension in Type 2 Diabetes**

Hypertension is common among adults with type 2 diabetes (T2DM). Data from the NHANES 1999–2004 survey indicate that overall, over 70% of adults with prevalent T2DM have coexisting HTN, and that the frequency of HTN in that group has been increasing over the past decade (Suh et al. 2009). Indeed, a significant proportion of adults with newly diagnosed T2DM are already hypertensive at the time of diagnosis (Hypertension in Diabetes Study Group 1993). Hypertension in adult T2DM is often poorly controlled, with only about 30% of patients achieving the recommended target BP of

<130/80 (Suh et al. 2009). Consequently, adults with T2DM have a high rate of stroke and other severe cardiovascular disease manifestations, and premature death from cardiovascular causes is common (Mugo et al. 2007).

Until recently, given that T2DM in children was rare, data were scarce on the prevalence of HTN in children and adolescents with T2DM. However, with the emergence of T2DM in the adolescent population, particularly in North America, where incident cases of diabetes mellitus in some ethnicities and age groups are now as likely to be T2DM as they are T1DM, (Lawrence et al. 2009; SEARCH for Diabetes Group 2006) better data are emerging. In a 2006 analysis of data from the SEARCH for diabetes in youth study in the USA, among approximately 2100 children aged 3–19 years old with diabetes, the prevalence of BP above the 90th percentile or treatment with antihypertensive medications was 22% among those with T1DM versus 73% among those with T2DM. However, there were fewer than 100 patients with T2DM in the study sample (Rodriguez et al. 2006). Subsequent data from SEARCH showed that in a cohort of 410 youth with T2DM of mean duration of 18 months, 23.7% were hypertensive, with similar rates in the children under 12 as compared with those older than 12 years (Rodriguez et al. 2010). In multivariate analysis, only higher BMI was independently associated with HTN, suggesting that weight, independent of glycemic control, is important in the development of HTN in children. Data from an Australian study (Eppens et al. 2006a) showed that, similar to the SEARCH data from the United States, 36% of youths with T2DM (mean duration of 1.3 years) were hypertensive and 28% had evidence of microalbuminuria. These complication rates are much higher than seen in children with T1DM, despite a much shorter duration of disease in those with T2DM. Similar rates of HTN were also reported in the broader Asia Pacific pediatric T2DM population, and in that study the same association between BMI and HTN in established T2DM as that seen in SEARCH was found (Eppens et al. 2006b).

Finally, data from the TODAY study, a randomized multicenter clinical trial of treatment options for T2DM in adolescents and youth (TODAY), showed that in 704 youth with T2DM with a mean duration of diabetes of less than 8 months, 26.3% had a BP  $\geq$ 90th percentile and 13.6% had a BP  $\geq$ 95th percentile (Copeland et al. 2011). No differences were seen in these rates by ethnic group; however, boys with T2DM had higher rates of HTN than girls. In 2012, results became available after the minimum 2-year treatment period had concluded for all participants (TODAY Study Group 2012). Using BP  $\geq$ 95th percentile as the cutoff, a further 22% of the study patients developed HTN over the study period, and by the end of the 2-year follow-up period more than one third of participants in all treatment groups were hypertensive. No significant difference was found in the rates of HTN appearance in any of the three study treatment groups (Table 3). As in SEARCH, higher BMI was a risk factor for HTN (TODAY Study Group 2013).

Microalbuminuria was found in 6.3% at baseline and increased to 16.6% at the end of the study period (TODAY Study Group 2013). Diagnosis of microalbuminuria was not significantly between treatment arms, sex, or race/ethnicity (TODAY Study Group 2013). Higher levels of hemoglobin A1c were significantly related to risk of developing microalbuminuria (TODAY Study Group 2013).

These aforementioned studies primarily use BPs obtained in clinic rather than by ambulatory BP monitoring (ABPM). In a study of obese minority adolescents with and without T2DM utilizing ABPM Ettinger et al. (2005) found ambulatory HTN in 39% of those with T2DM, compared to only 8% of those without T2DM. Nearly all ABPM variables, including mean wake and sleep BP, and wake and sleep BP loads

(Urbina et al. 2008), were significantly higher in the T2DM group. Blunted nocturnal dipping, however, was common in both groups, affecting 58% of those with T2DM and 42% of those without T2DM, suggesting that blunted dipping may be an early manifestation of elevated cardiovascular risk in obese youth whether or not T2DM has developed. Alarming, 40% of the adolescents in the Ettinger et al. study had microalbuminuria, (Ettinger et al. 2005) suggesting that as in adults and as mentioned above, there is early development of cardiovascular disease in pediatric patients with T2DM.

Large-scale studies should now be conducted to assess the importance of HTN as a risk factor in adolescents with T2DM prospectively. The TODAY study was the first prospective study to include relevant BP data in an intervention trial; however, the study was designed to assess the effect of interventions not directed at HTN, but rather at glycemic control (TODAY Study group 2012). It does not seem surprising that rates of new cases of HTN were high in the study, given the high failure rate of each arm on HbA1c criteria. Incorporation of ABPM and consensus definitions of HTN into such studies will be needed to produce the most accurate assessment of early cardiovascular disease in T2DM.

In summary, HTN and other complications of diabetes are common and appear early in the course of T2DM. As high albumin excretion rates are seen in the MetS in children, it seems likely that subclinical renal damage may occur before overt T2DM appears. Given the typically lower reported rates of HTN in childhood T1DM, providers caring for youth with diabetes will need specific education about the importance of BP control and the risk of nephropathy in childhood T2DM.

**Table 3** Prevalence of HTN\* at baseline and new cases of HTN from the TODAY Study

	Overall	Metformin alone	Metformin + Rosiglitazone	Metformin + lifestyle intervention
Cases at Baseline (%)	11.6	12.1	11.6	11.1
New cases during study (%)	22.2	24.6	22.7	19.2

\*Defined as BP  $\geq$  95<sup>th</sup> percentile, SBP  $\geq$ 130 mmHg, or DBP  $\geq$  80 mmHg  
Adapted from reference 33



## Pathophysiology

A detailed discussion of the mechanisms underlying the development of HTN in patients with the MetS or T2DM is beyond the scope of this chapter, but key points deserve emphasis. Since there is considerable overlap with obesity-related HTN, the interested reader should see ► [Chap. 6, “Insulin Resistance and Other Mechanisms of Obesity Hypertension.”](#) Additionally, reviews of the pathophysiology of obesity-related HTN in adults (Mugo et al. 2007; Aghamohammadzadeh and Heagerty 2012; Redon et al. 2009; Hall 2003) are pertinent to pediatric patients with either the MetS or T2DM.

Insulin resistance is clearly the major pathophysiological mechanism involved in the development of HTN in both the metabolic syndrome and T2DM. Insulin resistance in the obese is a mechanism evolved for limiting weight gain (Landsberg 2001). Through the effects on the blood vessels, the heart, and the kidneys, hyperinsulinemia and sympathetic activation exert a “prohypertensive effect” (Landsberg 2001). Several lines of evidence link hyperinsulinemia with increased sympathetic nervous system (SNS) activation and HTN, including the finding of elevated levels of plasma catecholamines, and abrogation of HTN after adrenergic blockade (Rocchini 2002; Tentolouris et al. 2006). While there are likely multiple mechanisms involved in the activation of the SNS in the MetS and T2DM, hyperinsulinemia is one of the most important (Esler et al. 2001).

There are many other mechanisms by which hyperinsulinemia may contribute to the development of HTN. Insulin resistance is associated with altered renal handling of sodium, with increased sodium reabsorption and expansion of plasma volume. It is likely that increased renal sympathetic nerve activity is responsible, at least in part, for this effect (Esler et al. 2001). Subsequent activation of the hypothalamic-pituitary-adrenal axis and elevated circulating levels of aldosterone, which have been demonstrated in salt-sensitive obese adolescents, may also be involved (Rocchini et al. 1989). Importantly, these effects of hyperinsulinemia on renal sodium handling

can be reversed with weight loss (Rocchini et al. 1989).

Insulin resistance and hyperinsulinemia are also associated with maladaptive changes in vascular structure and function. Although insulin when infused directly into local vascular beds acts as a vasodilator (Anderson et al. 1991) through nitric oxide-dependent mechanisms (Scherrer et al. 1994), in hypertensive subjects this effect is probably offset by insulin-associated vasoconstriction, perhaps via increased sympathetic nervous activity (Anderson et al. 1991; Reaven et al. 1996) associated with an inflammatory cascade in vascular smooth muscle and activation of the mitogen-activated protein kinase (MAPK) pathway associated with stress responses (Schulman and Zhou 2009). Impaired vasodilation in response to insulin infusion has been demonstrated in obese adults (Laakso et al. 1990). Insulin may also act to stimulate vascular smooth muscle proliferation in resistance vessels via activation of the local renin-angiotensin system (Kamide et al. 2000), thereby leading to increased peripheral vascular resistance due to vascular medial hypertrophy. In this way, hyperinsulinemia would lead to HTN by increasing systemic vascular resistance. These mechanisms are supported by studies demonstrating altered vascular structure and function in obese youth with and without T2DM (Urbina et al. 2009).

Adipose tissue is now known to be a metabolically active organ, and not just a static depot for energy storage. Many pro-inflammatory cytokines and hormones are secreted by adipose tissue, and may participate in inflammatory responses to acute and chronic stress. High calorie diets, obesity, and the metabolic syndrome are associated with high rates of secretion of these products including TNF $\alpha$ , IL-6, and nonesterified fatty acids (Kahn et al. 2006). HTN is associated with increased systemic and vascular inflammatory responses, and inhibition of mediators of the inflammatory cascade in a rat model of HTN and endothelial dysfunction reduces BP and insulin resistance (Shoelson et al. 2006; Zhou et al. 2010).

Activation of the renin-angiotensin-aldosterone system (RAAS) also characterizes obesity-related HTN. Many components of the RAAS

have been shown to be increased in obesity HTN in adults (Aghamohammadzadeh and Heagerty 2012), but data in youth have not been consistent. In obese adolescents with or without T2DM, plasma renin activity (PRA) has been positively correlated with BMI, but negatively correlated with 24-hour ambulatory BP (Shatat and Flynn 2011). These results contrast prior work done in children with primary HTN which demonstrated a positive correlation between PRA and ambulatory BP (Flynn and Alderman 2005). While further studies are needed, activation of the RAAS is likely present in many, if not all, patients with obesity-related HTN, and as will be discussed later, may be targeted as one component of treatment of these patients.

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## Therapy

Since elevated BP is one of the defining criteria of the MetS, and since many patients, including adolescents, may already be hypertensive at the time of diagnosis of T2DM, treatment of elevated BP will be required in many, if not most, children and adolescents diagnosed with either the MetS or T2DM. Given the common pathophysiology of HTN in both the MetS and T2DM, treatment of both conditions will be discussed collectively.

### Role of Nonpharmacologic Therapy

Weight loss, aerobic exercise and dietary modifications have all been shown to reduce BP successfully in children and adolescents, and are therefore recommended as primary treatment in children with obesity-related HTN (National High Blood Pressure Education Program Working Group on High Blood Pressure in C & Adolescents 2004) (Also see ► Chap. 43, “Nonpharmacologic Treatment of Pediatric Hypertension”). Studies in obese adolescents have demonstrated that weight loss not only decreases BP but importantly for those with the MetS or T2DM also improves other cardiovascular risk factors such as dyslipidemia and insulin resistance (Reinehr and Andler 2004; Rocchini et al. 1988; Williams et al. 2002).

In studies in which an approximate 10% reduction in body mass index was achieved, short-term reductions in BP were in the range of 8–12 mmHg. Recent data on the effects of weight loss surgery in adolescents confirms the CV benefits of weight loss (Inge et al. 2016). Unfortunately, weight loss is difficult and frequently unsuccessful. Additionally, even intensive efforts at weight loss in childhood may be followed by recidivism and an increased prevalence of adverse consequences of obesity in adulthood (Togashi et al. 2002). However, identifying a medical complication of obesity such as the MetS or T2DM may potentially provide the necessary motivation for patients and families to make the appropriate lifestyle changes.

Similarly, exercise training in children and adolescents does have a beneficial effect on BP (Torrance et al. 2007). Regular exercise training not only reduces BP but also improves other markers of early cardiovascular disease (Farpour-Lambert et al. 2009). However, cessation of regular exercise is generally promptly followed by a rise in BP to preexercise levels. Aerobic exercise activities such as running, walking, or cycling are usually preferred to static forms of exercise in the management of HTN. Many children may already be participating in one or more appropriate activities and may only need to increase the frequency and/or intensity of these activities to produce a reduction in their BP. At the very least, the amount of time spent in sedentary activities such as television viewing should be restricted to <2 h/day (Daniels et al. 2005). Increasing physical activity may not only reduce BP but can help with weight loss and/or maintenance, and has been demonstrated to be more effective than treatment with metformin in preventing the development of T2DM (Knowler et al. 2002).

For best BP reduction and weight control results, exercise should be combined with dietary changes. Such an approach has been shown to improve markers of insulin resistance in obese adolescents (Ben Ounis et al. 2008). The combination of dietary changes and exercise training may also improve vascular function in addition to reducing BP (Ribeiro et al. 2005).

Dietary modification in the management of HTN in children and adolescents has received much attention. Nutrients that have been examined include sodium, potassium, and calcium, as well as folate, caffeine, and other substances. Manipulation of sodium intake has received extensive study (Falkner and Michel 1997). Many authors have noted that the typical dietary sodium intake of children and adolescents, at least in the United States, far exceed any nutritional requirements for sodium, even for growing children. Trials of dietary sodium restriction in hypertensive children and adolescents have produced mixed results, with some studies showing no benefit, and others showing a modest reduction in BP in obese but not in lean adolescents (Falkner and Michel 1997; Rocchini et al. 1989). Thus, dietary sodium restriction may have a role in treatment of children and adolescents with the MetS or T2DM, a substantial proportion of whom are likely to be salt-sensitive. The National High Blood Pressure Education Program Working Group suggests a target sodium intake of 1200 mg/day in young children and 1500 mg/day in older youth (National High Blood Pressure Education Program Working Group on High Blood Pressure in C & Adolescents 2004).

Increases in both potassium and calcium intake have been shown to have antihypertensive effects in hypertensive children and adolescents. A 2-year trial of potassium and calcium supplementation in hypertensive, salt-sensitive children demonstrated that this combination significantly reduced systolic BP (Mu et al. 2005). Therefore, a diet that is low in sodium and enriched in potassium and calcium may be more effective in reducing BP than a diet that restricts sodium alone.

An example of such a diet is the so-called Dietary Approaches to Stopping Hypertension (DASH) diet, which has been shown to have an antihypertensive effect in adults with HTN, even in those receiving antihypertensive medication (Appel et al. 1997; Appel et al. 2006). The basic elements of the DASH eating plan are straightforward to apply to the treatment of hypertensive children, especially if accompanied by counseling from a pediatric dietitian. A study in a population of mostly obese adolescents with

either prehypertension or stage I HTN confirmed that a DASH-type eating plan was effective in reducing BP (Couch et al. 2008). The DASH diet also incorporates higher intake of micronutrients such as folate, which may have an antihypertensive effect, as well as measures designed to reduce dietary fat intake, an important strategy given the frequent presence of both HTN and dyslipidemia in children and adolescents with the metabolic syndrome or T2DM.

### **Cardiovascular Effects of Oral Hypoglycemic Agents**

Through adult studies, it has become apparent over recent years that many of the agents used to improve insulin sensitivity in persons with the MetS or T2DM also have beneficial cardiovascular effects. Although treatment with these agents will not obviate the need for antihypertensive medications in many patients, their potential impact on BP deserve consideration.

Metformin, which is widely used in patients with T2DM, is a biguanide antihyperglycemic drug that lowers hepatic glucose production, lowers plasma free fatty acid levels, and improves insulin sensitivity, primarily by increasing peripheral glucose uptake in skeletal muscle and adipose tissue (Vague 2003; Wellington 2005). The landmark United Kingdom Prospective Diabetes Study (UKPDS) trial found that metformin treatment led to a 39% reduction in risk of heart attack over 10 years in diabetic patients. Studies in rats with streptozotocin-induced diabetes have demonstrated that metformin reduces BP and restores aortic endothelial function (Majithiya and Balaraman 2006). Human studies, however, have not uniformly demonstrated a significant effect of metformin on BP in adults with type 2 diabetes. Metformin has also been associated with weight loss in adolescents with insulin resistance when accompanied by adherence to a lifestyle intervention (Love-Osborne et al. 2008).

The Carotid Atherosclerosis: Metformin for insulin ResistAnce (CAMERA) trial was an adult study designed to investigate the effect of metformin on changes in carotid intima-media

thickness (cIMT; an established marker of atherosclerosis) in nondiabetic persons with heart disease taking statins (Preiss et al. 2014). One hundred and seventy-three patients were randomly assigned to metformin or matching placebo for 18 months (Preiss et al. 2014). After 18 months, no improvement in cIMT or the extent of atherosclerotic plaque in the carotid arteries was noted in patients taking metformin (Preiss et al. 2014). The average cIMT increased significantly in both groups (0.024 mm per year for metformin, 0.017 mm for placebo) (Preiss et al. 2014). However, metformin significantly reduced all measures of adiposity (body weight [by over 3 kg], body fat, body mass index, and waist circumference) and improved in other risk factors for the development of type 2 diabetes (e.g., lower insulin and HbA1c) (Preiss et al. 2014). Major cardiovascular outcome trials are needed to conclusively assess metformin's cardiovascular effects in people without type 2 diabetes – such trials are underway at present. However, CAMERA suggests that metformin has limited impact on important cardiovascular risk factors when patients are already on a statin (Preiss et al. 2014).

Manzella et al. randomized 128 adult patients with T2DM to either metformin or placebo and examined the effect of metformin on BP and the SNS. While metformin treatment resulted in a significant improvement in cardiac sympathovagal balance as assessed by heart rate variability, no changes were noted in mean arterial BP (Manzella et al. 2004). In another study, metformin was given for 12 weeks to obese subjects with T2DM previously managed either with dietary therapy alone or sulfonylurea monotherapy. Although metformin, either as monotherapy or in combination with a sulfonylurea, improved glycemic control, there was no significant effect on BP (Abbasi et al. 2004). Finally, Stakos et al. randomized participants with insulin resistance and normal glucose tolerance to receive glipizide 5 mg/day, metformin 500 mg/day, or placebo for 2 years. Patients in the metformin and placebo groups had a mild but significant decrease in systolic and diastolic BP, while the glipizide group had a mild but nonsignificant decrease in BP (Stakos et al. 2005). Clearly, metformin alone

will be insufficient treatment for HTN in the metabolic syndrome or T2DM, but it may have some beneficial cardiovascular effects. Data from the TODAY study, referenced earlier, indicate that approximately one third of patients were hypertensive by the end of the trial, despite all participants being treated with metformin (TODAY Study Group 2012).

Rosiglitazone, a thiazolidinedione, binds to the peroxisome proliferators-activated receptor-gamma (PPAR- $\gamma$ ), a transcription factor that regulates the expression of genes that involved in glucose production, transport and utilization in the liver, adipose tissue, and muscle (Wellington 2005). Rosiglitazone has been shown to improve vascular function and ameliorate BP in hypertensive transgenic mice (Ryan et al. 2004). Negro et al. compared the effects of rosiglitazone and metformin versus metformin alone on BP and metabolic parameters of diabetic patients (Negro et al. 2005). After 1 year of treatment with both rosiglitazone and metformin, a significant reduction of systolic and diastolic BP was demonstrated by ambulatory BP monitoring. In a similar study, rosiglitazone treatment produced a significant reduction in ambulatory BP that was correlated with improvements in insulin sensitivity (Sarafidis et al. 2004). Rosiglitazone has also been studied in combination with metformin with or without the addition of glimeperide, a second-generation sulfonylurea, in hypertensive patients with type 2 diabetes (Derosa et al. 2005). Patients were randomized to treatment with either metformin + glimeperide or to metformin + rosiglitazone. Mean BP was not significantly improved at any time in the group that received glimeperide + metformin; however, BP significantly improved at 12 months in those who received rosiglitazone + metformin. The antihypertensive effect of rosiglitazone appeared to be mainly related to decreased insulin resistance and improvement in endothelial function.

Pioglitazone, another thiazolidinedione, was studied in patients with T2DM who had abnormal nocturnal BP on ambulatory BP monitoring. Patients were randomized to either metformin + placebo or to metformin + pioglitazone. After 8 weeks of treatment, the metformin + pioglitazone group

had reduced nocturnal BP values which were independent of changes in metabolic parameters (Negro et al. 2004). While robust data on the BP effects of thiazolidinediones in children are lacking, the TODAY study suggests that, in youth with T2DM, the addition of rosiglitazone to metformin did not confer a greater benefit with regard to HTN risk, when compared with metformin alone (TODAY Study Group 2012). These minimal beneficial effects on cardiovascular risk may not outweigh the known adverse effect profile of this class of agent.

Although not approved for use in children in the United States, the incretin-based therapies such as the glucagon-like peptide (GLP-1) analogues and Dipeptidyl peptidase-4 (DPP-4) inhibitors may ultimately prove beneficial. GLP-1 is secreted by the L cells of the intestine and augments glucose-dependent insulin secretion, suppresses glucagon, induces satiety, and slows gastric emptying. GLP-1 appears to have effects on BP as well. Evidence exists that GLP-1 and its analogues induce vasodilation, and clinical studies of GLP-1 analogues with long duration of action have examined their effects on BP in humans (Brown 2012). One study of exenatide, a GLP-1 analogue, in adults with T2DM showed beneficial effects on systolic BP when compared with insulin or placebo (Okerson et al. 2010), but these results may be confounded by weight loss, a known, likely beneficial, side effect of incretin-based therapies. The effects of inhibition of DPP-4, the enzyme responsible for the rapid degradation of GLP-1, on BP are even less clear. While early trials using DPP-4 inhibitors in adults with the MetS were not designed to examine the effect on BP(80), their effects on HTN may be dynamic and depend on interaction with the RAAS (Marney et al. 2010). A case report presented a middle-aged female with type 2 diabetes had assessment of arterial stiffness before and after vildagliptin treatment (Cosensio-Martin et al. 2015). Applanation tonometry (AT) of the radial artery is a noninvasive method that indirectly assesses arterial stiffness by calculating the central SBP and the augmentation index (AIx) (Cosensio-Martin et al. 2015). This case suggested the DPP-4 inhibitor was associated

with improvements in arterial stiffness parameter (central SBP) in a hypertensive and diabetic patient, which shows a glucose-independent beneficial cardiovascular effect of this group of drugs (Cosensio-Martin et al. 2015). The relevance of DPP-4 inhibitors to pediatric HTN is unclear, as available studies are preliminary, and none have been conducted in children or adolescents.

Acarbose is a glucose oxidase inhibitor that delays the absorption of glucose, resulting in a reduction of postprandial blood glucose levels. The STOP-NIDDM (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus) trial examined the effect of acarbose on the progression of patients with impaired glucose tolerance (IGT) to diabetes, HTN, and cardiovascular disease (Chiasson 2006). After a mean follow-up of 3.3 years, treatment with acarbose resulted in a 25% relative risk reduction in the development of T2DM, a 34% risk reduction in development of new cases of HTN, and a 49% risk reduction in the development of cardiovascular events. Another study by Rachmani et al. examined the effect of 24 weeks of acarbose treatment on insulin resistance in obese hypertensive patients with normal glucose tolerance (Rachmani et al. 2004). Insulin resistance improved in the acarbose group; however, BP declined equally in the two groups.

Canagliflozin is of the gliflozin class or subtype 2 sodium-glucose transport (SGLT-2) inhibitors and is a newer treatment for type 2 diabetes in adults (Sha et al. 2014). Blocking this transporter causes up to 119 g of blood glucose per day to be eliminated through the urine (Sha et al. 2014). Additional water is eliminated by osmotic diuresis, resulting in a lowering of blood pressure (Sha et al. 2014). Sha et al. examined the effects of canagliflozin on glycemia and blood pressure (Sha et al. 2014). Canagliflozin also reduced both fasting plasma glucose and HbA1c (Sha et al. 2014). Reductions in body weight and blood pressure were observed after 3 months of treatment (Sha et al. 2014).

Although mainly limited to studies conducted in adults, these data suggest that some of the agents used to improve insulin sensitivity in patients with the MetS and/or T2DM may have

additional benefits in lowering BP, but results from the largest of these studies, TODAY, are unconvincing with regard to HTN. It is also pertinent to point out that metformin remains the only FDA approved oral medication for managing T2DM in youth. No large pediatric studies have been performed using insulin-sensitizing therapy that directly addresses BP as the primary end point. Rather, they use, unsurprisingly, glycemic targets such as glycosylated hemoglobin as the outcome variable of interest and are thus designed and powered accordingly, with BP as a secondary variable. Further studies designed and conducted with BP as a primary outcome might provide a clearer picture of the effects of these agents on cardiovascular risk in youth. However, available data suggest that it is unlikely that treatment with these agents alone would be sufficient to control HTN, making combination treatment with antihypertensive drugs necessary in many affected children and adolescents.

## Antihypertensive Drug Therapy

### Indications for Antihypertensive Drug Therapy

Even with successful weight loss, exercise, dietary changes, and use of the oral hypoglycemic agents discussed above, antihypertensive medications will be needed in many patients with the MetS or T2DM in order to achieve goal BP. Despite the potential theoretical benefits of initiation of drug therapy early in life, it is important to recognize that the long-term consequences of untreated HTN in a child or adolescent remain unknown. Similarly, there is a lack of data on the benefits of therapy in the pediatric age group, as well as possible long-term effects of antihypertensive medications on growth and development, which add further uncertainty to the decision to initiate drug treatment. However, the knowledge that accelerated cardiovascular disease occurs commonly in adult patients with the MetS or T2DM and that early evidence of this is often already present in adolescence adds impetus for starting drug therapy early in young patients with these diagnoses.

As recommended by the NHBPEP (National High Blood Pressure Education Program Working Group on High Blood Pressure in C & Adolescents 2004), definite indications for initiating pharmacologic therapy in a child or adolescent include the following:

- Stage 2 hypertension (see Table 1)
- Symptomatic hypertension
- Secondary hypertension
- Hypertensive target-organ damage
- Diabetes (types 1 and 2)
- Persistent hypertension despite nonpharmacologic measures

Thus far, although it might seem reasonable to add the presumptive diagnosis of the MetS as an additional indication for initiating drug therapy, no consensus organization has yet endorsed such an approach, probably because of the uncertainties surrounding the definition of the MetS in pediatrics as discussed earlier. At the very least, children and adolescents with the MetS and BP above the prehypertensive range who do not adhere to or respond to a reasonable (6–12 month) trial of nonpharmacologic measures should probably be prescribed antihypertensive medications, given the high risk of progression of the MetS to frank diabetes, and given the increased risk of development of atherosclerosis in these patients.

### Choice of Antihypertensive Medication

The general topic of drug therapy in childhood HTN, including recommended drug doses, is covered in detail in ► [Chap. 44, “Pharmacologic Treatment of Pediatric Hypertension,”](#) so the following discussion is limited to specific aspects pertinent to the MetS and T2DM. One of the key general principles of treatment of HTN is consideration of comorbidities that may preferentially favor one class of drug over another. The best example of this principle can be found in the JNC-7 Report (Chobanian et al. 2003), which highlighted a list of “compelling indications” that, based upon the results of large-scale clinical trials, favored the use of specific drug classes.

Unfortunately, a similar evidence base is lacking for pediatric patients, as studies including pediatric and adolescent patients with these comorbid conditions have not been conducted.

Probably the most important issue to consider in the selection of an antihypertensive agent in the pediatric patient with the MetS or T2DM is the effect of that drug class or specific agent on insulin sensitivity. Alpha-adrenergic blockers, for example, are well-known to improve insulin sensitivity and have been advocated for use in treatment of HTN in patients with impaired glucose tolerance and/or frank diabetes (Giorda et al. 1995; Inukai et al. 2004). Alpha blockers lower triglyceride and free fatty acid levels, and have no effect on total, high-density or low-density cholesterol (Inukai et al. 2004), important considerations given the common finding of dyslipidemia in the MetS and T2DM. The benefits of alpha blockade have also been demonstrated in a study of the combined alpha- and beta-blocker carvedilol, which effectively reduced BP without worsening selected metabolic parameters in adults with the MetS (Uzunlulu et al. 2006). Unfortunately most alpha-blocking agents have not been systematically studied in children, so there is no available guidance on dosing.

Calcium channel blockers have also been demonstrated to have beneficial effects on insulin sensitivity in patients with essential HTN (Harano et al. 1995; Koyama et al. 2002). By extension, they would be appropriate for use in persons with the MetS. Even more encouraging is blockade of the RAAS with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). These agents have been shown to have either neutral or beneficial effects on glucose metabolism, and have the potential to prevent the development of diabetes in individuals with the MetS (Scheen 2004; Gillespie et al. 2005). Additionally, since the RAAS is likely activated in patients with obesity-related HTN (which would include the MetS and T2DM) (Mugo et al. 2007; Aghamohammadzadeh and Heagerty 2012; Redon et al. 2009; Hall 2003), there is a specific pathophysiological basis for using these agents. Some of the newer ARBs appear to activate PPAR- $\gamma$ , producing the beneficial effects of

the thiazolidinediones without the weight gain and other potential adverse effects associated with those agents (Pershad Singh 2006). Therefore, many authors recommend ACE inhibitors and ARBs as the first-line agents for treatment of HTN in patients with the MetS (Asfaha and Padwal 2005). Not to be overlooked is the effect that RAAS blockers have on ameliorating progression of diabetic nephropathy (Ritz and Dikow 2006), making these agents even more appropriate if there is concurrent microalbuminuria.

In contrast, diuretics and beta-adrenergic blockers are usually thought to have “diabetogenic” potential (Izzedine et al. 2005), and many authorities in adult HTN recommend that they should probably be avoided as initial agents in patients with coexisting metabolic syndrome (Verdecchia et al. 2005). This position is supported by reanalysis of data from the ALLHAT study (Officers et al. 2002), which demonstrated a greater incidence of new-onset diabetes in the group treated with chlorthalidone as compared to those treated with amlodipine or lisinopril (Punzi et al. 2004). However, these results may have been the result of use of chlorthalidone in combination with the beta-blocker atenolol, which was the most commonly prescribed second-line agent in ALLHAT. The combination of a thiazide diuretic and a beta blocker is thought to be particularly diabetogenic (Mason et al. 2005).

However, other authors have argued that the adverse effects of diuretics and beta blockers have been overstated, and that these classes of agents can be used judiciously in such patients, particularly as second-line agents, given the imperative to control BP and prevent the development of more significant cardiovascular disease (Asfaha and Padwal 2005). Data to support this approach was recently published in a study that compared the short-term metabolic effects of thiazide diuretics with those of the potassium-sparing diuretic amiloride and the  $\beta$ -1 selective adrenergic blocker nebivolol (Stears et al. 2012). Patients who received amiloride or nebivolol had normal responses to an oral glucose tolerance test, whereas those treated with a thiazide had impaired glucose tolerance. Similar results have been reported for the  $\beta$ -1 selective adrenergic blocker

metoprolol (Falkner and Kushner 2008). Thus, it may be reasonable to include selected nonthiazide diuretics and cardioselective adrenergic blockers as part of the treatment regimen in patients with diabetes or MetS.

The most recent pertinent clinical trial data addressing the choice of antihypertensive agents in diabetic patients comes from the ACCOMPLISH (Avoiding Cardiovascular Events through COMbination Therapy in Patients Living with Systolic Hypertension) trial (Weber et al. 2010). Adult patients with diabetes who were randomized to the ACE inhibitor benazepril plus amlodipine had a lower rate of cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization) than those randomized to benazepril plus hydrochlorothiazide. As previously noted, the cardiovascular endpoints that were studied in ACCOMPLISH (and other large-scale trials in adults) occur rarely, if at all, in the pediatric age group. However, in the absence of studies conducted in children and adolescents, these adult trials do provide insights into treatment that can be adapted into the care of our younger population.

### Therapeutic Goals

In adults with complicated HTN such as that seen in T2DM, a lower treatment goal (130/80) has traditionally been recommended than in those with uncomplicated HTN (140/90), (2) based on the results of large-scale clinical trials. More recent expert opinion, however, has shifted away from this approach (James et al. 2014). Lacking large-scale trials in pediatric HTN, the National High Blood Pressure Education Program (NHBPEP) has developed a similar recommendation for children: for children with uncomplicated primary HTN and no hypertensive target-organ damage, goal BP should be <95th percentile for age, gender, and height, whereas for children with secondary HTN, diabetes, or hypertensive target-organ damage, goal BP should be <90th percentile for age, gender, and height. (National High Blood Pressure Education Program Working

Group on High Blood Pressure in Children & Adolescents 2004) Recent pediatric guidelines issued by the European Society of Hypertension suggest lower BP goals than those in the Fourth Report, and also recommend frequent use of ambulatory BP monitoring to guide therapy (Lurbe et al. 2016). Treatment goals in the new US childhood hypertension guidelines are summarized in the Appendix.

There are no data to guide the treatment of patients with metabolic syndrome who do not have established T2DM. Given the chances that these patients will ultimately develop T2DM, we would recommend treating to the 90th percentile in children and young adolescents with the MetS. In older hypertensive adolescents aged  $\geq 18$  years with the MetS or T2DM, current adult guidelines should be followed.

### Role of Bariatric Surgery

In adult patients with severe obesity, bariatric surgery has emerged as possibly the most effective approach to weight loss. Bariatric surgery has also been shown to have beneficial effects on the cardiovascular complications of obesity, particularly in patients with T2DM (Van Gaal and De Block 2012). Bariatric surgery may be more effective in youth than in adults in reversing the metabolic complications of obesity, and these improvements in metabolic status may precede clinically significant weight loss once such surgery is done. (104) Further data are required, but in an uncontrolled study HTN resolved in 14 severely obese adolescents who underwent bariatric surgery (Silva et al. 2012). However, there are many questions about the role of bariatric surgery in the management of obesity in the young (Ingelfinger 2011) that will need to be addressed before this approach could be routinely recommended as part of the management of HTN in an obese child or adolescent with the MetS or T2DM. Adolescents undergoing weight-loss surgery at five US centers are being prospectively followed. Patients undergoing Roux-en-Y gastric bypass or sleeve gastrectomy were included (Inge et al. 2016). Changes in body weight, coexisting conditions, cardiometabolic risk factors, and weight-related quality of life and postoperative



complications were examined through 3 years after the procedure (Inge et al. 2016). At 3 years after the procedure, the mean weight had decreased by 27% in the total cohort, by 28% among participants who underwent gastric bypass, and by 26% among those who underwent sleeve gastrectomy (Inge et al. 2016). After 3 years after the procedure, remission of type 2 diabetes occurred in 95% of participants who had had the condition at baseline, remission of abnormal kidney function occurred in 86%, remission of prediabetes in 76%, remission of elevated blood pressure in 74%, and remission of dyslipidemia in 66% (Inge et al. 2016).

## Conclusions

The high prevalence of obesity in children and adolescents is now known to be accompanied by numerous complications, including the MetS and T2DM. Although there is still some uncertainty regarding the optimal definition of the MetS in the young, its core components, most notably HTN, are readily detectable in MetS and T2DM. HTN in obese children with or without T2DM is characterized by abnormalities on ABPM and may be diagnosed earlier using this technique compared to use of office BP measurements. Management of such children should begin with intensive lifestyle modifications, and aggressive treatment targeted at glucose control should follow. However, effects on BP are likely to be modest in the absence of weight loss. Antihypertensive drugs are frequently necessary, and consideration should be given to the agent's effect on insulin sensitivity. In addition to better studies of drug therapies, there is clearly a need for increased efforts to prevent childhood obesity so that these complications can be avoided altogether.

## Cross-References

- ▶ [Insulin Resistance and Other Mechanisms of Obesity Hypertension](#)
- ▶ [Nonpharmacologic Treatment of Pediatric Hypertension](#)

- ▶ [Pharmacologic Treatment of Pediatric Hypertension](#)
- ▶ [Primary Hypertension in Children](#)
- ▶ [Stress and Salt Sensitivity in Childhood Hypertension](#)
- ▶ [Value of Routine Screening for Hypertension in Childhood](#)

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## Abstract

Hypertension in children is not as common as in adults and its prevalence in the pediatric population is about 3–4%. Recent reports have highlighted an increasing prevalence of childhood hypertension, likely due to childhood obesity. Given the global burden of hypertension, identification and management of primary hypertension is beneficial to the individual child and has important implications for society as well, particularly since tracking studies have established that adult primary hypertension has its antecedents during childhood. Studies on the pathophysiology of primary hypertension in children are limited; however, evidence suggests that the proposed multifactorial and complex genetic, environmental, and biological interactions involved in the development of hypertension in adults provide a basis to understand hypertension in children as well. In comparison to younger children who mostly have secondary hypertension, primary hypertension is much more common in adolescents. Primary hypertension is diagnosed in children after a selective workup to rule out any underlying secondary causes. Early identification and management of elevated BP in the

pediatric population is important to decrease the risks for end-organ injury in both the pediatric and adult population.

## Keywords

Primary hypertension • Children • Hypertension • Pathophysiology • Risk factors • Obesity • End-organ damage

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## Introduction

Worldwide, hypertension affects nearly a billion people at an estimated prevalence of 40% in adults aged 25 or older, and complications related to hypertension are responsible for nearly nine million deaths every year (World Health Organization 2013). In the USA, the diagnosis of hypertension accounts for nearly 70 million hypertensive adults (one in three adults has hypertension) and is also the most common diagnosis for outpatient physician visits and prescription drugs (Egan et al. 2010; Nwankwo et al. 2013). Hypertension is a global public health problem, and primary hypertension is believed to have its antecedents during childhood. Studies have shown that the relationship between arterial pressure and mortality is quantitative; the higher the pressure, the worse the prognosis (Pickering 1974). Therefore, it is important that those providing care to children approach the issue of hypertension both as a societal challenge and as a disease affecting discrete individuals.

## Definitions and Techniques

The recent American Academy of Pediatrics (AAP) guideline as well as the European and Canadian consensus statements (Harris et al. 2016; Lurbe et al. 2016; Flynn et al. 2017) provide guidelines for the diagnosis, evaluation, and management of high blood pressure (BP) in children. As per the current recommendations, systolic and/or diastolic BP readings  $\geq 95$ th percentile for sex, age, and height, or  $\geq 130/80$  in teens  $\geq 13$  years old on three separate occasions are required for diagnosing hypertension. The most widely used and recommended nomograms for BP in children are those provided in the Fourth Task Force Report (Harris et al. 2016; Lurbe et al. 2016; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). While the US normative BP data are derived from a multiethnic sample of healthy children, the lack of BP nomograms across

different ethnicities, or from specific geographic regions, is a potentially important limiting factor in improving our understanding of pediatric hypertension across different societies.

BP in children and adolescents is currently further categorized into elevated BP stage 1 hypertension and stage 2 hypertension. The most recent classification scheme from the AAP is discussed in detail in the Appendix.

Once hypertension is confirmed, evaluation of hypertensive patients to rule out secondary hypertension is essential to diagnosing primary hypertension. Table 1 summarizes various recommendations for evaluating confirmed hypertension in children (Harris et al. 2016; Lurbe et al. 2016; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). The majority of children with hypertension have a normal baseline evaluation (Baracco et al. 2012; Kapur et al. 2010; Kapur and Baracco 2013). Children with hypertension and normal baseline evaluation could be further categorized as (Kapur and Baracco 2013):

- (a) Young children with stage 1 or 2 hypertension: There is no age cutoff to categorize young children, but additional evaluation as recommended in the consensus statements (Table 1) should be considered in children  $< 10$ – $12$  years (Baracco et al. 2012; Kapur and Baracco 2013; Brewer 2009).
- (b) Obese adolescents with stage 2 hypertension or nonobese adolescents with several cardiovascular risk factors and stage 1 or stage 2 hypertension: Additional evaluation (Table 1) to be done in patients with resistant or uncontrolled hypertension, hypertensive emergencies or urgencies, or ambulatory blood pressure monitoring (ABPM) findings suggestive of secondary hypertension.
- (c) Nonobese adolescents with no risk factors and stage 1 or 2 hypertension: These patients could undergo further evaluation based on clinical suspicion/experience in managing pediatric hypertensive patients (Kapur and Baracco 2013; Baracco et al. 2012).

**Table 1** Evaluation of children diagnosed with hypertension

	Fourth Task Force Report	European	Canadian
<b>Baseline evaluation</b>			
Serum electrolytes, BUN, creatinine, complete blood count, urinalysis	All hypertensive patients	All hypertensive patients	All hypertensive patients
Renal ultrasound	All hypertensive patients	All hypertensive patients	All hypertensive patients
ECHO	All hypertensive patients	All hypertensive patients	All hypertensive patients
Fasting lipid and glucose	Overweight + Prehypertension	All hypertensive patients	All hypertensive patients
	All hypertensive patients		
	Chronic renal failure		
	Family history of hypertension or CVD		
Urine culture	All hypertensive patients	–	–
Chest X-ray, ECG	–	All hypertensive patients	–
Urine protein/microalbumin	–	All hypertensive patients	All hypertensive patients
<b>Additional evaluation</b>			
Plasma renin activity, serum aldosterone	Young stage 1 hypertension	Recommended additional screening tests	–
	All stage 2 hypertension		
Urine/plasma catecholamines, metanephrines	Young children with stage 1 hypertension	Recommended additional screening tests	–
	All children with stage 2 hypertension		
Urinary free cortisol Tc99 DMSA scan	–	Recommended additional screening tests	–
Plasma and urine steroid	Young children with stage 1 hypertension and all children with stage 2 hypertension	After results of screening tests are available	–
Renovascular imaging	Young children with stage 1 hypertension and all children with stage 2 hypertension	After results of screening tests are available	–

Renovascular hypertension (RVH) should be considered in children with (1) malignant hypertension, (2) uncontrolled or hypertension requiring multiple antihypertensives, (3) children with worsening end-organ damage, (4) ABPM findings suggestive of secondary hypertension, or (5) children with syndromes associated with increased risk for RVH such as neurofibromatosis 1/2, tuberous sclerosis, Williams syndrome, and Marfan's syndrome (Kapur and Baracco 2013; Marks and Tullus 2012; Tullus et al. 2008).

Some researchers have questioned the validity of the current definition of hypertension in children (Collins and Alpert 2009) defined by a statistical cutoff point in the continuum of BP nomograms using a rigorous study protocol (Falkner 2010; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). A diagnosis of hypertension is consistent with an increased risk of cardiovascular morbidity and mortality that becomes increasingly prevalent



as BP increases. A pragmatic definition of hypertension would be the level of systolic BP and/or diastolic BP above which recognizable morbidity (such as stroke, heart failure, or chronic renal failure) occurs. Currently, there are no data that adequately define this in children. This is in contrast to adults, wherein outcome data in terms of increased cardiovascular morbidity or mortality is used to define normal versus elevated BP.

As reviewed by Collins et al. (Collins and Alpert 2009), the recommendation of using three BP readings to diagnose hypertension may in fact underdiagnose hypertension in children. Currently there are no data to demonstrate that two BP readings are better or inferior in identifying hypertensive children. The same review (Collins and Alpert 2009) also highlights the limitations of using the statistical definition of hypertension for minority ethnic groups, such as African Americans, who may have a higher prevalence of hypertension and associated end-organ damage. The use of Gaussian distribution curves would diagnose hypertension at much higher levels in these groups and possibly delay indicated interventions (Collins and Alpert 2009). However as reviewed by Flynn and Falkner (Flynn and Falkner 2009), the fundamental question that remains unanswered is what BP is non-physiological and whether this represents an absolute value or a percentile cutoff.

The importance of obtaining accurate BP readings in diagnosing hypertension has been emphasized repeatedly by all consensus statements (Flynn et al. 2017; Harris et al. 2016; Lurbe et al. 2016; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). There are many confounding factors in BP measurement in children, including cuff size, the number of measurements, type of instruments used, patient position (supine or sitting), and the choice of sound [Korotkoff (K) 4 vs. K 5] used for defining diastolic BP (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). Many of these issues are discussed in detail in ► **Chap. 13, “Methodology of Casual Blood Pressure Measurement.”**

Ambulatory blood pressure monitoring (ABPM) is currently recommended for evaluation of hypertension (Harris et al. 2016; Lurbe et al. 2016; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004) and is being increasingly used in diagnosing and evaluating hypertension in children (Sorof and Portman 2000; Flynn and Urbina 2012). The advantages of ABPM include identification of white coat and masked hypertension from true hypertension, diurnal BP variability in normal and hypertensive populations, identification of dipping versus non-dipping BP patterns, and diagnosis of secondary hypertension (higher SBP load, 24 h DBP load) (Flynn 2002; Lurbe et al. 2016).

According to the European Society of Hypertension, ABPM in children is recommended in (Lurbe et al. 2016; Flynn et al. 2014):

1. Hypertension diagnosis, prior to starting antihypertensive treatment or in children with risk factors for hypertension such as obesity, sleep apnea, diabetes mellitus, chronic kidney disease, tissue or organ transplant, or genetic syndromes with increased risk for hypertension (such as Turner, neurofibromatosis 1, tuberous sclerosis)
2. During hypertension treatment, for evaluating refractory hypertension, assessment of BP control in relationship to organ damage, or in children with symptoms of hypotension
3. Clinical trials of antihypertensive treatment in children with reduction in a number of study patients
4. In conditions of autonomic dysfunction such as catecholamines secreting tumors or autonomic dysfunction

The use of ABPM in children with high BP continues to be limited in comparison to adults (Flynn and Flavin 2012). Standardized guidelines for obtaining and interpreting ABPM readings in children and adolescents are provided by the American Heart Association (Urbina et al. 2008), and a recent update

includes hypertension categorization based on diastolic BP which was missing from the earlier recommendations (Flynn et al. 2014). Interpretation of the ABPM data is limited in part by the small cohort of children ( $n = 1100$ ) included in the normative dataset, lack of ethnic diversity in the cohort, minimal diastolic BP variability, and limited BP on children with height less than 140 cm (Flynn 2011; Urbina et al. 2008). Cost is another limitation to utilizing ABPM in pediatric settings. ABPM is often not a covered benefit in children. Based on Medicare's current reimbursement rate of around \$18.19, 190–220 ABPM studies will recover the initial starting cost of the commonly used ABPM monitor (Spacelabs 90207; Spacelabs Medical, Hawthorne, CA, along with the software, costs around \$3500–\$4000) (Kapur 2013). ABPM is discussed in depth in ► [Chap. 16, “Ambulatory Blood Pressure Monitoring Methodology and Norms in Children.”](#)

In conclusion, the diagnosis of primary hypertension (Table 2) in children is a multistep process. This includes (1) multiple BP measurements on different visits, (2) interpretation of these BP

readings in terms of the published nomograms, and (3) a detailed history, physical examination, and laboratory evaluation tests (Bucher et al. 2013). Appropriate investigations are necessary to rule out secondary hypertension and assess for end-organ damage.

## Prevalence

Recent screening studies from the USA and other countries have reported similar prevalence rates of 3–5% for hypertension in the pediatric population (Antal et al. 2004; Cao et al. 2012; de Rezende et al. 2003; Genovesi et al. 2005; Kardas et al. 2005; McNiece et al. 2007; Saleh et al. 2000; Sharma et al. 2010; Sorof et al. 2004; Steinhorsdottir et al. 2011), trend to the higher end of the range reflect higher BP associated with rise in childhood obesity (Flynn 2013; Redwine and Daniels 2012). However, it is difficult to estimate the exact worldwide burden of pediatric primary hypertension due to regional differences in definition criteria and normative values for diagnosing hypertension in children.

Prevalence of elevated BP/prehypertension based on single BP measurements (in contrast to diagnosing hypertension involving at least three BP measurements) in children is reported at 4–17% (Bucher et al. 2013; Flynn 2013; Redwine and Daniels 2012). Based on a study by Hansen et al., prevalence of prehypertension on repeated BP measurements is 3.4% similar to prevalence of hypertension in children (Hansen et al. 2007). However, it is important to note that BP is continuously changing. Therefore the implications to cardiovascular health of almost 30% of the population with an elevated BP on at least one occasion and estimated 75% crossover across BP categories between sessions (Acosta et al. 2012; Redwine and Daniels 2012) though unknown may be significant.

Blood pressure measurements collected with a similar protocol in children included in the National Health and Nutrition Examination Survey (NHANES) are representative of the general

**Table 2** Criteria to use in diagnosing primary hypertension in children

<i>Primary criteria</i>
An average of two to three readings of systolic BP and/or diastolic BP exceeding the 95th percentile for age, gender, and height repeated three times over a 2–3-month period
Ambulatory blood pressure measurements over a 24-h period that exceed the 95th percentile for age-matched controls and/or a failure to find a nocturnal dip
Unable to identify a known secondary cause of hypertension
<i>Supportive criteria</i>
Stage 1 hypertension on presentation
Children obese on presentation (BMI >95th percentile)
Family history of hypertension
Idiopathic hypertension associated with high, normal, or low PRA
Abnormal response to mental stress
Evidence of end-organ effect, fundoscopic changes, cardiac enlargement by electrocardiogram and/or echocardiogram (suggestive of long-standing hypertension)

US population and provide information on the BP trends over time. Analysis of the NHANES data has shown:

- Significant differences in both mean systolic and diastolic BP after adjusting for BMI between NHANES III (1988–1994) and NHANES 1999–2000 (Muntner et al. 2004)
- Increasing prevalence of prehypertension and hypertension when comparing (a) NHANES III and NHANES 1999–2002 (Din-Dzietham et al. 2007) or (b) NHANES III and each of NHANES 1999–2002 and NHANES 2003–2006 (Ostchega et al. 2009)
- Twenty-seven percent increase in odds of elevated BP in children between NHANES III and NHANES 1999–2008, after accounting for differences in age, sex, ethnicity, BMI, waist circumference, and Na intake (Rosner et al. 2013)

More recent reports have highlighted the effects of childhood obesity on the prevalence of hypertension and prehypertension in children and adolescents (Flynn 2013; Redwine and Daniels 2012). The frequency of hypertension appears to increase as the severity of obesity increases. The effects of obesity on childhood hypertension are highlighted in publications of case series of children referred to tertiary centers, in whom up to 91% are now found to have primary hypertension (Flynn 2013; Kapur et al. 2010).

It is important to note that identification of elevated BP readings is paramount to diagnosing and evaluation of children with elevated BP. In two separate studies (Brady et al. 2010; Hansen et al. 2007), most BP elevations were not recognized by providers. Poor recognition was most influenced by the absence of obviously elevated BP, obesity, family history of cardiovascular disease, or evaluation by a less experienced provider (Brady et al. 2010).

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## Incidence

Data on the incidence of hypertension in children are scarce. The analysis of the National Childhood Blood Pressure database (BP recorded at 2- and

4-year intervals) has shown an incidence rate of 7% per year in adolescents with prehypertension. However, the diagnosis of hypertension was based on single BP readings, which is not consistent with current guidelines.

More recent data from Redwine et al. in nearly 1000 adolescents (Redwine et al. 2012) has reported an incidence rate of 0.7% per year for hypertension diagnosed according to recommended guidelines. In adolescents who were prehypertensive at the initial screening, the rate was 1.1% per year as compared to a rate of 0.3% per year in adolescents who were normotensive at the initial screening. The highest risk for progression at 6.6% per year was seen in adolescents with elevated BP at all three visits. As highlighted in a recent review (Redwine and Falkner 2012), these findings could potentially translate into nearly half a million hypertensive adolescents after 5 years.

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## Predictors of Primary Hypertension

*BP tracking* refers to the stability of repeated BP measurements over a period of time; thus, if tracking is present, children with elevated BP are more likely to become hypertensive as adults. Increased strength of tracking is reported in the presence of a family history of hypertension, increased body weight, or increased left ventricular mass (Beckett et al. 1992; Chen and Wang 2008; Katz et al. 1980; Shear et al. 1986). This is indicative of the interaction between the genetic and environmental factors influencing BP. The Muscatine Study, for example, has demonstrated that primary hypertension in young adults has much of its origin during the childhood years (Lauer and Clarke 1989). Although the strength of the tracking phenomenon has been questioned (Toschke et al. 2010), tracking studies are important as they underscore the need for early identification and treatment of elevated BP, given the current global scenario of increased cardiovascular disease-associated morbidity along with the worldwide increase in childhood and adult obesity. An analysis from the Fels Longitudinal Study (Sun et al. 2007) (non-Hispanic whites only) has

reported that the earliest differences in systolic BP occurred at 5 years of age in boys and 8 years of age in girls. The BP cutoffs (boys <102/65 and girls <92/62 at 5 years, boys <104/64 and girls <102/64 at 14 years, boys <115/67 and girls <104/64 at 18 years) as developed by the random effects model in the analysis are lower than the 50th percentile and therefore not considered high risk per Fourth Task Force Report recommendations (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). Systolic and not diastolic BP above the cutoff values as reported in the study was associated with increased risk for developing hypertension with or without the metabolic syndrome (Sun et al. 2007).

Children and adolescents with primary hypertension may present with either stage 1 or stage 2 hypertension (Baracco et al. 2012; Kapur et al. 2010). Primary hypertension in children is often associated with a family history of hypertension or other cardiovascular disease. Other comorbid conditions associated with primary hypertension in children, which increase the risk for cardiovascular disease, include abnormal lipid profile, glucose intolerance, and sleep abnormalities.

White-coat hypertension (WCH) or isolated office hypertension is defined as office BP readings  $\geq$ 95th percentile but with normal values outside the clinical setting. The reported prevalence of WCH in children varies based on the study population, BP measurement methods (ABPM versus non-ABPM), and diagnostic criteria. WCH prevalence has been reported at a rate (a) 0.6–1% in school-based screening or outpatient pediatric clinic (Steinthorsdottir et al. 2011; Lurbe et al. 2005), (b) 7% in ABPM studies done in a tertiary clinic (Halbach et al. 2016), (c) 32% among children with diabetes (Sulakova et al. 2009), (d) 35% in children being evaluated for persistently elevated casual BP and 44% in children with a family history of primary hypertension (Hornsby et al. 1991), and (e) 46% in children referred to a tertiary pediatric nephrology center (Ramaswamy et al. 2016). The prevalence of white-coat hypertension is higher

when the office values reveal borderline or mild hypertension and much lower with moderate or severe hypertension (Sorof et al. 2001). Similar to adults, a retrospective study in children has shown that WCH is possibly a prehypertensive condition with increased left ventricular mass and progression to sustained hypertension (Kavey et al. 2007). Increased urinary excretion of cortisol and endothelin in adolescents with WCH identifies a group with distinct metabolic abnormalities (Vaindirlis et al. 2000). Since urinary endothelin is derived from the kidney, these findings support a dysregulation of renal function. It is possible that WCH in children represents two populations: one that is destined to develop primary hypertension (prehypertensive) (Matthews et al. 1993) and one that will remain normotensive outside clinical setting.

Masked hypertension (normal clinic BP and elevated ambulatory BP) has been reported to have cardiovascular risk similar to sustained hypertension (Verberk et al. 2008). Diagnosis of masked hypertension can only be made by ABPM, but it should be suspected in children with previously elevated clinic BP readings, lack of correlation between clinic BP, and evidence of end-organ damage and obese individuals with non-dipper ABPM pattern (Flynn et al. 2014). In a study by Lurbe et al. of 592 children aged 6–18 years, in 34 patients with masked hypertension (median follow-up 37 months), 47% had persistent or sustained hypertension. These patients had a higher left ventricular mass index (LVMI) and a higher percentage with left ventricular mass index above the 95th percentile than normotensive controls (Lurbe et al. 2005).

The patient phenotype most commonly associated with primary hypertension in children is adolescents with overweight, obesity, or elevated BMI (Feig and Johnson 2003). Metabolic syndrome is reported in 10–15% of the children with hypertension (Litwin et al. 2007). Hyperuricemia, hypertriglyceridemia, low HDL cholesterol, glucose intolerance, and insulin resistance are the biochemical abnormalities frequently reported in children with primary hypertension (Litwin et al. 2013a).

## BP Homeostasis and Pathophysiology of Hypertension

A wide variety of factors involved in regulating BP are discussed in detail in Part I, “Regulation of Blood Pressure and Pathophysiologic Mechanisms of Hypertension” of this book. However, a brief overview of the factors determining BP is presented here, as it is necessary to understand the steps involved in the generation and persistence of primary hypertension (Table 3). While most of the discussions below are based on adult and animal studies, evidence from tracking studies suggests that the proposed multifactorial and complex genetic, environmental, and biological interactions involved in development of hypertension in adults provide a basis to understand hypertension in children as well.

The factors involved in increasing BP during the generation and maintenance of primary hypertension are often different. In one form, the increase in cardiac output (CO) during its early stages has been attributed to a hyperkinetic circulation characterized by increased heart rate (HR), cardiac index and forearm blood flow secondary to increased sympathetic tone, and cardiac contractility (Julius et al. 1991; Sorof et al. 2002). Fixed persistent primary hypertension is characterized by an increase in total peripheral resistance (TPR) and a return to a normal CO. In the second form, early hypertension is characterized by increased left ventricular (LV) mass, as also reported in normotensive offspring of hypertensive parents. These observations raise the possibility that repeated neural stimulation and upregulation of cardiac receptors may be the

primary event in the onset of primary hypertension (Korner et al. 1992).

The two main renal mechanisms involved in sodium and water excretion and thus control of BP are *pressure natriuresis* (volume) and the *renin-angiotensin-aldosterone system (RAAS)* (vasoconstriction). Each mechanism, in turn, is influenced by multiple other factors which may increase or decrease the relative contribution of volume and/or vasoconstrictor components of BP. *Pressure natriuresis* is the increased urinary excretion of sodium and water in response to elevated arterial pressure to maintain BP by regulating body volume. Despite wide variations in sodium intake, the kidneys are able to maintain a constant BP. The RAAS influences both elements of the BP formula. The central role of the RAAS in hypertension has recently been reviewed elsewhere (Simoes and Flynn 2012).

Genetic renal defects linked with *abnormal sodium homeostasis* in primary hypertension include increased efferent arteriolar tone leading to increased sodium reabsorption, congenital reduction in the number of nephrons and filtering surface (Brenner et al. 1988), nephron heterogeneity (Sealey et al. 1988), and non-modulation that involves abnormal adrenal and renal responses to angiotensin (ANG) II infusions (Hollenberg et al. 1975). Single-gene disorders that affect renal sodium handling are discussed in more detail in ► **Chap. 7, “Monogenic and Polygenic Contributions to Hypertension.”**

Recent research in animal models has highlighted the role of the medullary circulation in pressure natriuresis and pathogenesis of hypertension. Increased medullary blood flow is associated with increased vasa recta capillary pressure, loss of osmotic gradient, and thus increased natriuresis. Blunting of the pressure natriuresis due to alteration of the balance between medullary vasodilators (nitric oxide, endothelin) and medullary vasoconstrictors (vasopressin and angiotensin II) has been linked to hypertension (Mattson 2003).

*Nephron heterogeneity* (Sealey et al. 1988) has also been proposed as an underlying mechanism for blunted natriuresis in hypertensive patients. The heterogeneity is attributed to a smaller group of ischemic nephrons with

**Table 3** Basic blood pressure formula and its physiologic transformation to hypertension

1. Pressure equals flow times resistance
2. BP = volume times resistance
3. BP = CO times total peripheral resistance
4. BP = flow (preload + contractility) × resistance (arteriolar functional contraction + vessel anatomical changes), for example, BP = flow × resistance
5. Hypertension = a net increase in CO and/or increased peripheral resistance

markedly increased renin secretion leading to angiotensin II-mediated arteriolar constriction and vascular remodeling. This is supported by reports of focal afferent arteriolar narrowing (common) along with juxtaglomerular cell hyperplasia associated with increased renin secretion in patients with primary hypertension.

*Eutrophic vascular remodeling* (Schiffrin and Touyz 2004) is the pathologic alteration of the precapillary resistance vessels characterized by a reduction in the vessel lumen associated with increase in media to lumen ratio. This vascular remodeling is increasingly identified as the predominant change in hypertensive patients and attributed to multiple factors such as increased (a) myogenic tone of the vessel wall, (b) matrix deposition, and (c) growth toward the vessel lumen with apoptosis in the periphery and altered smooth muscle motility of the vessel wall (Intengan and Schiffrin 2001; Schiffrin and Touyz 2004). The RAAS through ANG II appears to be significantly involved in the vascular remodeling as evidenced by animal studies and human studies reporting improvement in small arterial function with ACE/ARB and not by other antihypertensives (Intengan and Schiffrin 2001; Kaplan 2009; Schiffrin and Touyz 2004).

*Sympathetic nervous system (SNS) activity* can function as an initiator and as a secondary contributing factor to elevated BP. Impaired circulatory homeostasis and heightened vascular reactivity in hypertensive patients in comparison to normotensives as indicated by increased BP, tachycardia, and flushing in response to noxious stimuli provide evidence for SNS overactivity. In children, SNS activation may be the primary mechanism for hypertension without an underlying cause and may be the link to elevated BP in patients with WCH. An imbalance between parasympathetic and sympathetic activity and increased muscular sympathetic nerve activity has been reported in patients with WCH (Yamaguchi and Flynn 2009; Koch et al. 1999; Neumann et al. 2005).

*Perinatal influences:* Critical development period theory proposes developmental stages which are more sensitive to certain environmental factors and thus lead to propagation of certain

genetic information. As reviewed by Kunes et al. (2012), these changes are not detected immediately but after a certain delay (“late consequences of early alterations”). Barker’s hypothesis and subsequent studies provide support for the intra-uterine period being a critical period for development of primary hypertension (discussed in detail in ► Chap. 8, “Perinatal Programming of Arterial Pressure”) (Barker 1992; Seckl 1997).

*Genetics:* At least 25–30 candidate genes have been suggested as contributors to the hypertensive process by affecting critical factors involved in the vasoconstriction and/or volume elements of the BP formula (Table 4). Current evidence links genes controlling plasma angiotensinogen (AGT) with risk for hypertension, while no conclusive association is reported with the ACE gene polymorphisms (Harrap et al. 2003; Sethi et al. 2003). The angiotensinogen M235T genotype has been associated with increase in angiotensinogen levels and increased risk for hypertension (Sethi et al. 2003). The theory of impaired genetic homeostasis postulates (Neel et al. 1998) that the mismatch between genes involved in the regulation of BP and the acculturated changes in our society accounts for the recent increase in documented hypertension. Synchronicity, a process by which growth spurts are associated with increases in BP, may be accelerated in genetically prone hypertensive individuals (Akahoshi et al. 1996). Allometric dysfunction, a process by which somatic and renal growths fail to match each other, might lead to hypertension if environmental factors enable excessive non-genetically determined growth to occur (Weder and Schork 1994). The failure of renal vascular remodeling to occur during fetal and postnatal life might alter the expected decreases in the activity of RAS and/or sodium regulatory mechanisms. Premature telomere shortening, a process associated with normal aging, may lead to hypertension (Aviv and Aviv 1997). Finally, perturbation in neural development of the sympathetic nervous system and/or cardiac  $\beta$ 1-receptors may predispose newborns to develop a hyperkinetic circulation and, therefore, hypertension (Julius et al. 1979).

*Systemic inflammation:* Ongoing systemic inflammation has been reported in primary

**Table 4** Hypertension and gene studies

<i>Genome-wide association study (GWAS)</i>	
Weaknesses – large sample size is needed to detect meaningful association, higher study costs, need for stricter quality control, and handling of large databases	
<i>Linkage reported in most of the chromosomes; however, there is little current clinical application</i>	
WTCC (Wellcome Trust Case Control 2007), Saxena R (Diabetes Genetics Initiative of Broad Institute of Harvard et al. 2007), Levy D (Levy et al. 2007), Kato N (Kato et al. 2008), Sabatti C (Sabatti et al. 2009) – no significant genome-wide association	
Global BPGen study (Newton-Cheh et al. 2009) – eight regions with genome-wide significance in chromosomes	
CHARGE study (Levy et al. 2009) – significant genome-wide associations between 13 SNPs with SBP, 20 SNPs with DBP, and 10 SNPs with hypertension	
<i>Genome search meta-analysis (GSMA) – meta-analysis of the GWAS</i>	
Levy D (Levy et al. 2009)	Global BPGen and CHARGE meta-analysis of 8 SNPs on chromosomes; 12 (ATP2B1), 10 (CYP17A1), 11 (PLEKH7), 12 (SH2B3), 10 (CACNB2), 15 (CSK-ULK3), 12 (TBX3-TBX5), 3 (ULK4) with significant association with SBP/DBP/ hypertension SNP ATP2B 12q 21–23 associated with significant association with SBP/hypertension
Wu X (Wu et al. 2006)	No locus achieving significant linkages; suggestive linkage at 2p14 and 3p14.1
Koivukoski (Koivukoski et al. 2004)	Significant association with DBP and hypertension at 2p12-q22.1, 3p14.1-q12.3
Liu (Liu et al. 2004)	No genome-wide significant linkage to hypertension
<i>Candidate gene analysis</i>	
Strengths – known pathophysiological processes associated with hypertension are studied at genetic level, and animal data is available on these genes, compared to GWAS that are low cost	
Weaknesses – hypertension TN is polygenic, and individual genetic contribution to hypertension phenotype may be small, cannot evaluate gene/environment interaction, and has less chance for identifying newer genetic pathways linked to hypertension	
G-protein system (Zhu et al. 2006) – G-protein $\beta$ -subunit (GNB3) gene C825T polymorphism, G-protein receptor kinase 4 (GRK4) gene, G $\alpha$ s subunit (GNAS) gene	
$\alpha$ -Adducin (ADD1) gene, Gly460TRP polymorphism (Manunta and Bianchi 2006)	
Polymorphisms of CYBA gene encoding p22 phos subunit of the NADPH oxidase system (San Jose et al. 2008)	
Renal sodium transporters (Gong and Hubner 2006); SCNN1B gene encoding $\beta$ -subunit of ENaC transporter $\beta$ -ENaC G589s polymorphism, SLC9A3 gene encoding NHE 3 exchanger in proximal tubule	
RAAS genes (Pereira et al. 2008; Rudnicki and Mayer 2009): (1) AGT gene for angiotensinogen M235T, A-6G, A-20C polymorphisms, (2) ACE deletion/insertion (D/I) polymorphism intron 16 and ACE 2 gene, (3) type 1 angiotensinogen II receptor gene (AT <sub>1</sub> R), (4) CYP11B2 aldosterone synthase gene C344T polymorphism	
Genes linked with changes in vascular tone (Sheppard 2010); <i>adrenergic receptors</i> ; (1) $\alpha$ 1a gene 347 Cys polymorphism, (2) $\alpha$ 2a gene Dral polymorphism, (3) $\alpha$ 2b gene Glu 301–303 deletion variant, (4) $\alpha$ 2c insertion/deletion polymorphism <i>nitric oxide (NO)</i> endothelial NO synthase gene on chromosome7 G849T polymorphism	
<i>Adenosine monophosphate deaminase 1 (AMP-1)</i> (AMPD 1) gene polymorphism, <i>endothelin-1</i> gene polymorphisms, and G-protein polymorphisms	
Mitochondrial gene mutations (Gong and Hubner 2006; Watson et al. 2001); mitochondrial NADH dehydrogenase 3 gene A10398G mutation	
<i>Large-scale candidate gene studies</i>	
Sober S (Sober et al. 2009), Padmanabhan S (Padmanabhan et al. 2010), Tomaszewski M (Tomaszewski et al. 2010) – no significant association with BP candidate genes	
Johnson T (Johnson et al. 2011) replicated SNP for angiotensin locus AGT and ATP2B1 locus of other studies and reported other novel loci	

hypertension. Smoking, drugs, diet, and other comorbid conditions could lead to increased inflammation especially in hypertensive adults. Higher serum concentration of inflammatory markers such as highly sensitive C-reactive

protein (hsCRP) and chemokines (RANTES, MIP1 $\beta$ ) in children with primary hypertension in comparison with normotensive children has been reported (Litwin et al. 2010). The relationship between increasing serum sICAM-1 (intercellular

adhesion molecule) and IL-6 (interleukin 6) levels and higher BP in apparently healthy adult males indicates that higher BP may stimulate systemic low-grade inflammation (Chae et al. 2001).

Studies have shown upregulation of genes involved in inflammatory responses, antioxidative defense, apoptosis, vesicular trafficking of molecules among cellular organelles, and renin-angiotensin system in leucocytes of untreated hypertensive adults in comparison to treated hypertensive patients (Chon et al. 2004; Coppo et al. 2011). The study by Chon et al. also reported a downregulation of these genes upon treatment (Chon et al. 2004). Another study did not show any difference in gene expression in relation to disease stage or antihypertensive therapy (Timofeeva et al. 2006). In children with primary hypertension, increased expression of ACE and CD14 and downregulation of angiotensinogen (AGT) and AT<sub>2</sub> type 1 receptor (AT<sub>2</sub>R1) in peripheral leucocytes have been reported (Litwin et al. 2013a, b). Furthermore, Litwin et al. have also identified a downregulation of these genes with non-pharmacologic treatment in adolescents (Litwin et al. 2013b).

A two-step, feed-forward paradigm in which hypertensive stimuli promote inflammation which promote further elevation in BP has been proposed (Harrison et al. 2011). Initially, central stimuli mediated by angiotensin II, sodium, and others lead to modest elevation in blood pressures and manifest clinically as the prehypertension stage. These modest BP elevations stimulate an inflammatory response, possibly by generating neoantigens that activate T cells. The inflammatory response leads to entry of effector-like T cells and macrophages into the perivascular fat and the kidney, leading to release of cytokines and other inflammatory mediators which in association with angiotensin II, catecholamines, and salt cause vascular and renal dysfunction, vasoconstriction, vascular remodeling, a shift in the pressure-natriuresis curve and sodium retention, and sustained hypertension. The inflammatory response in hypertension is also influenced by oxidative events (Harrison et al. 2011). Immune activation and hemodynamic injury via matrix metalloproteinases (MMP) and its tissue

inhibitors (TIMP) lead to cellular remodeling and fibrosis. A recent meta-analysis reported that MMP-9 and TIMP-1 correlate with left ventricular hypertrophy (LVH) in adult hypertensive patients (Marchesi et al. 2012).

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## Risk Factors Involved in Childhood Primary Hypertension

### Non-modifiable Risk Factors

#### Age and Gender

Children have lower BP levels in comparison to adults, but the levels progressively increase with age, with a linear rise from 1 to 13 years. This increase is related more to body size than age. Primary hypertension is the most common cause of hypertension in older children especially in the postpubertal group. The prevalence of hypertension and prehypertension is greater in boys than girls (Dasgupta et al. 2006). Also, in girls BP rises rapidly between 6 and 11 years as compared to 12–17 years, while the opposite is seen in boys. The male preponderance of high BP persists till 50 years of age, when BP levels in women again exceed men's (Bender et al. 2004).

Lever and Harrap hypothesized that primary hypertension may be linked with accelerated somatic maturation (Lever and Harrap 1992). It is proposed that arterial wall hypertrophy and insulin resistance may be linked with accelerated biological maturation, leading to elevated BP (Lever and Harrap 1992; Litwin et al. 2013a). Studies reporting (a) accelerated bone age in children with elevated BP (Katz et al. 1980), (b) growth spurt related with a significant rise in BPs in boys (Halldorsson et al. 2011; Kulaga et al. 2011), (c) adult males with highest growth velocity between ages 8 and 13 and increased risk of hypertension in comparison with males who had lowest growth velocity (Halldorsson et al. 2011), (d) increased risk for metabolic syndrome (MS) and visceral obesity in fourth decade in females with menarche at younger age (Kivimaki et al. 2008), and (e) advanced skeletal maturation in hypertensive children in comparison with healthy controls closely matched for age, sex,



and BMI (Pludowski et al. 2009) provide support to the hypotheses.

### **Race and Ethnicity**

The prevalence of primary hypertension is clearly influenced by race and ethnicity (Coroni-Huntley et al. 1989). Native Americans have the same or higher rate of primary hypertension as Hispanics who have the same or lower BP than Caucasians. The prevalence of hypertension in African Americans (AA) is twice that of whites, has an earlier onset, and is associated with more end-organ damage. These differences are most likely quantitative (Flack et al. 2002) for the characteristics of the hypertensive process are similar in blacks and whites when corrected for age, cardiovascular and renal damage, and level of BP (Flack et al. 1999). African Americans have higher sleep and less dipping in their nighttime ABPM values than age-matched whites (Harshfield et al. 1994). African Americans experience a greater degree of renal global, segmental, and interstitial sclerosis than whites at an earlier age, despite having similar BP and degrees of proteinuria (Cruickshank et al. 1985; Marcantoni et al. 2002). In a study by Brady et al. (2010), AA children had a higher prevalence of overweight/obesity and left ventricular hypertrophy and had higher plasma renin activity than non-AA children. A recent report from the Bogalusa Heart Study highlighted that despite higher vagal tone at rest, there is a greater BP response to stressful stimuli in African Americans (Berenson et al. 2011). The researchers also suggested that racial contrasts suggest, in part, that effects of lipoproteins may be greater in Caucasians, whereas the effects of excess BP variability, sodium intake and other environmental effects result in more cardiovascular damage in AA (Berenson et al. 2011). This association emphasizes the need for prevention of risk factors at an early age (Berenson et al. 2011).

### **Genetics and Family History**

Up to 40% of hypertension is attributable to genetic factors indicating increased risk for hypertension in genetically related individuals (Mongeau et al. 1986). However, it is important to note that the interaction between genes and a

permissive environment is essential for the development of elevated BP. Genome-wide association study (GWAS) has identified the association between common/new genetic variants and BP/hypertension (Table 4). The novel insight into disease pathology from these associations has not translated to clinical utility. Such differences may reflect environmental factors, the influence of other genes, evolutionary diversion (race and ethnicity), and study design and/or technical issues (Table 4). In the future, individual genetic information will help in early identification of high-risk groups for targeted preventive measures and pharmacotherapy based on individual disease pathways with low risk for adverse effects.

### **Modifiable Risk Factors**

#### **Obesity**

Worldwide, childhood obesity with its significant implications for immediate and future health is considered to be reaching epidemic proportions. Hypertension is more common among obese (pre-school, school, and adolescent) than nonobese children (Bucher et al. 2013; Flynn 2013; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). Increasing prevalence of childhood obesity has been associated with increasing diagnosis of primary hypertension in children (Bucher et al. 2013; Flynn 2013). The increasing diagnosis of primary hypertension in asymptomatic healthy children represents a significant and important shift in the current understanding of pediatric hypertension (Kapur et al. 2010).

Analysis of the World Health Organization (WHO) Global Database on Child Growth and Malnutrition predicts up to 60 million preschool children (9.1%) would be overweight and obese by 2020 at current rate of increase (de Onis et al. 2010). The association between obesity and the generation and persistence of childhood primary hypertension (Flynn 2013) has significant health implications. The relationship between elevated BP and weight begins in early childhood and has

been reported to occur as early as 5 years (Gutin et al. 1990). The Muscatine Study showed that changes in ponderosity over 11 years correlated directly with BP changes (Lauer and Clarke 1989). Increasing obesity has also been linked to increasing BP. A study involving 18,000 Minneapolis school children evaluated 10 years apart, reported an increase in childhood BMI over time was accompanied by an increase in systolic BP, and the association of weight and systolic BP was 2.5 times greater than that for height and systolic BP (Luepker et al. 1999). The association between obesity and hypertension is complex and various mechanisms have been proposed (Table 5). Obesity hypertension is discussed in more detail in ► Chaps. 6, “Insulin Resistance and Other Mechanisms of Obesity Hypertension,” and ► 21, “Obesity Hypertension: Clinical Aspects.”

### Sodium

It is estimated that since the Paleolithic period, the average sodium intake in the human diet has increased almost fivefold to approx 3400 mg/day, a level sufficiently high enough to enable high-BP expression in salt-sensitive individuals

(Eaton et al. 1988). Also, epidemiologic studies have shown that BP levels are higher in societies with high salt intake with higher BP associated with sodium intake above 100 meq/day (Elliott et al. 1996). He et al. (2008) have reported a nearly 50% increase in salt intake between the ages of 4 and 18 years. The study also reports significant association between salt intake and systolic BP which is independent of age, sex, body mass index, and dietary potassium. Analysis of the NHANES data by Rosner et al. (2013) reported significant increase in the prevalence of elevated BP for children  $>1.5 \times$  RDI for Na (OR = 1.36; 95% CI, 1.04–1.77;  $P = 0.024$ ) versus children with intake  $<$ RDI after controlling for both overall and central obesity. None of the other nutritional risk factors considered was significantly associated with the prevalence of elevated BP in multivariate analyses controlling for age, sex, race/ethnicity, BMI, and waist circumference (Rosner et al. 2013).

Experimental studies (Table 6) have shown that the amount and time of introduction of sodium in the diet of newborn rats influences the onset and persistence of hypertension. In human neonates, the ingestion of lower sodium (4 meq/L)

**Table 5** Mechanisms of hypertension in childhood obesity

1. Insulin resistance and hyperinsulinemia* leading to
a. Sympathetic nervous system activation
b. Renal sodium reabsorption
c. Impaired vasodilatation
d. Vascular smooth muscle proliferation
2. Hyperleptinemia leading to
a. Sympathetic nervous system activation
b. TGF- $\beta$ synthesis and increased type IV collagen leading to glomerulosclerosis
3. Elevated plasma renin activities and overall dysregulation of RAAS system
4. Increased pro-inflammatory cytokines such as TNF- $\alpha$ , IL-6 contributing to insulin resistance
5. Increased oxidative stress
6. Direct renal damage
a. Renal compression by peri-renal fat leading to reduced medullary blood flow, tubular compression leading to increased sodium reabsorption
b. Hyperfiltration injury
c. Increased TGF- $\beta$ 1 expression synthesis
7. Poor sleep quality and sleep apnea leading to sympathetic nervous system activation
8. Low vitamin D level

Adapted from (Bucher et al. 2013; Yamaguchi and Flynn 2009)

\*Unexplained insulin resistance in lean individuals with hypertension has been reported. Mechanisms for increased BP secondary to insulin resistance and hyperinsulinemia are hypothesized to be similar to those in obese individuals

**Table 6** Role of sodium in primary hypertension

Experimental evidence
High salt intake increases renal vascular vasoconstriction, catecholamine release, and NaK ATPase inhibitor ouabain, which in turn leads to increase in intracellular calcium and sodium
In salt-sensitive patients (obese, history of low birth weight) with primary hypertension, BP varies directly with changes in sodium intake
Decrease in salt intake in people with borderline high BP may prevent the onset of hypertension
The time and quantity of sodium administration to rats genetically predisposed to hypertension determine the onset and level of BP
Similar mother and offspring BP response to sodium restriction supports a genetic predisposition to salt sensitivity
Epidemiologic evidence
Significant correlations between salt intake and BP have been demonstrated in large population studies
Primitive isolated societies with naturally ingesting low-sodium diets do not develop hypertension, nor does BP rise with age
Primitive isolated societies increase their BP after being exposed to environments where excess sodium is ingested

containing formula after birth was associated with a 2.1-mm/Hg lower BP after 6 months (Hofman et al. 1983). Even though this difference did not persist a few years later, it is still possible that a lifelong effect may be seen.

Approximately 25–50% of the adult population is considered to be salt sensitive and exhibits increased BP fluctuation in association with slight increase in salt intake. Besides increasing with age, salt sensitivity has been reported in African American, obese, metabolic syndrome, and chronic kidney disease patient cohorts. Dietary sodium restriction is a recommendation in all guidelines (national and international) as a component of non-pharmacologic treatment for hypertension. A reduction in the average daily amount of salt or sodium intake from 3400 milligrams (mg) to 2300 mg (similar to the Dietary Guidelines for Americans, 2010 recommendations) may reduce cases of high blood pressure by 11 million and save 18 billion health-care dollars every year (Palar and Sturm 2009). In hypertensive children, the issue of salt restriction has not been fully evaluated in context of their requirements for growth and development.

### Exercise

Exercise provides a number of benefits: increased caloric expenditure, appetite suppression, and improved exercise tolerance. Serum cholesterol and triglyceride levels inversely relate to the level of exercise. Ekelund et al. (2012) in their study of nearly 21,000 children reported

improvement in cardiometabolic risk factors (waist circumference, fasting insulin, fasting triglycerides and HDL cholesterol, and resting systolic blood pressure) in association with moderate to vigorous physical activity. The improvement in risk factors was regardless of sex and age and also independent of the amount of sedentary activity. The latest WHO guidelines recommend 60 min of at least moderate-intensity physical activity in addition to activities of daily living (Andersen et al. 2011). Andersen et al. in their review of published literature of physical activity and cardiovascular risk factors in children have proposed that physical activity/intervention of at least 30-min duration, three times/week, and intensity sufficient to improve aerobic fitness is sufficient to decrease BP in hypertensive children (Andersen et al. 2011). Gopinath et al. (2012) have recently reported that different sedentary behaviors have a different effect on BP. According to their findings, each hour per day spent in watching TV or playing video games was associated with increase in diastolic BP, while similar time spent in reading was associated with decrease in systolic and diastolic BP. The BP response of hypertensive adolescents to exercise is similar to that of normotensive adolescents but starts and finishes at higher levels (Wilson et al. 1985). In adolescents, peak SBP >210 mmHg, and a rise in DBP with dynamic exercise, is occasionally used to determine the need for antihypertensive drug therapy (Jung and Ingelfinger 1993).

## Lipids

Prolonged elevation of cholesterol is strongly associated with an increased risk of coronary artery disease. Evaluations of the coronary arteries and aorta of 35 children and young adults dying from noncoronary artery disease events revealed fatty aortic streaks in 61%, coronary artery fibrous streaks and/or plaques in 85%, and raised plaques in 25% (Berenson et al. 1980). The extent of involvement correlated directly with total cholesterol and low-density lipoprotein (LDL) and, inversely, with the ratio of HDL to LDL cholesterol. Obesity is the most common cause of hypertriglyceridemia, often associated with a low HDL in adolescents. It is well known that inherited disorders of lipid metabolism increase the risk of early cardiovascular disease.

## Tobacco Smoking

Harmful effects of smoke exposure, active or passive, on the cardiovascular status have been shown in adults (Barnoya and Glantz 2005). Chronic smoking itself does not increase BP; it is associated with increased cholesterol levels and lower levels of high-density lipoprotein (HDL), which increase the risk of atherogenesis. Simonetti et al. (2011) have reported that environmental nicotine exposure as a consequence of parental (passive) smoking is associated with increased BP in children as young as 4–5 years of age. The study also reported a synergistic role wherein proportionately progressive increase in BP was noticed in cumulative association with other risk factors such as parental hypertension and obesity. Insufficient data are available to evaluate the association between electronic cigarettes (e-cigarettes) and adverse cardiovascular health (Steinberger et al. 2016). However, the use of e-cigarettes is also notably increasing, and studies including US children and adolescents admitting to the use of e-cigarettes report increased intention to smoke cigarettes among those who never smoked conventional cigarettes (Bunnell et al. 2015). A recent study reported that reduction or quitting of smoking by switching to e-cigarettes may lead to lower systolic BP 1 year from baseline, and this reduction is more apparent in smokers with elevated BP at baseline (Farsalinos et al. 2016).

## Stress

Stress of all types can increase BP. When compared to those with normal BP levels, greater increases in sympathetic nervous system and cardiovascular activity occur in offspring of hypertensive parents and in hypertensive individuals. Poverty, sociocultural factors, racial issues, and migration are also known to increase BP. The CARDIA study, a retrospective study that queried adults ( $n = 2739$  African Americans and Caucasians) about their childhood, proposed a model linking low childhood socioeconomic status and adverse early family environment marked by harsh parenting, poor emotional functioning, and poor health behaviors with elevated BP in young adults (age 33–45 years) (Lehman et al. 2009). Studies have also reported an association between psychosocial factors of childhood adversity such as physical abuse, sexual abuse, neglect, parental death, parental divorce, and hypertension (Post et al. 2013; Stein et al. 2010). Studies in adolescents have reported that changes in heart rate, BP, and cardiac output in response to psychological challenges under controlled lab conditions are significant predictors for the development of hypertension (Matthews et al. 2004; Stewart and France 2001; Treiber et al. 1997). Type A behavior is associated with increases in SBP, but not DBP (Siegel et al. 1983). Three models of psychosocial stress that might explain the genesis of primary hypertension are the defense defeat model, demand control, and lifestyle incongruity index (Pickering 1994). These models deal with issues such as fight flight, control, aggression, depression, subordination, the relationship between psychologic demands factored by the available latitude of decision-making, and differences between occupational and social class and achievement versus accomplishment.

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## Long-Term Effects of Hypertension in Children

Unlike adults, cardiovascular disease in the form of stroke or myocardial infarction does not manifest in children. However, recent studies have highlighted end-organ changes in children

secondary to sustained hypertension; for a detailed discussion, see ► Chap. 39, “Sequelae of Hypertension in Children and Adolescents.”

Tracking of high BP in childhood to adults is considered to be an important consequence of childhood hypertension (Bucher et al. 2013). In view of the high prevalence of hypertension in adults, high mortality due to cardiovascular causes and increased risk for renal, cardiac, and neurological sequelae associated with hypertension underscore the importance of identification and treatment of hypertension in children. A recent meta-analysis concluded that there is no direct evidence that screening for hypertension in children and adolescents reduces adverse cardiovascular outcomes in adults (Thompson et al. 2013). However, as reviewed by Samuels et al. (2013) and Rao (2016), these conclusions reflect a limitation of the clinical course of hypertension and thereby published literature rather than the lack of evidence. The meta-analysis discounts the results of studies highlighting (a) tracking of childhood BP into adults, (b) challenge of conducting studies wherein treated and untreated patients with elevated blood pressure diagnosed in childhood are followed for years till cardiovascular disease becomes manifest, and (c) similar vascular biology of pediatric and adult hypertension as evidenced by studies reporting cardiac and vascular end-organ damage, impaired vascular reactivity, and left ventricular hypertrophy secondary to hypertension in children (Bucher et al. 2013; Rao 2016; Samuels et al. 2013).

Left ventricular hypertrophy (LVH) as evidenced by elevated left ventricular mass index (LVMI) or increased thickness of the left ventricle has been most frequently reported as a consequence of childhood hypertension (Bucher et al. 2013; Lurbe et al. 2016; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). According to the European Society of Hypertension, the Devereux equation standardized to height ( $m^{2.7}$ ) should be used. Elevated LVMI is defined as  $LVMI > 0.38.6 \text{ g/m}^{2.7}$  (>95th percentile; norms based on small study cohorts) (Daniels et al. 1995; Lurbe et al. 2016). Prevalence of LVH ranging from 14% to 42% has been reported

reflecting lack of standardized definition in view of absence of large normative data (Lurbe et al. 2016). Increased risk for LVH has been reported with elevated BMI, obesity, and male gender (Matteucci et al. 2006). LVH has also been reported in patients with WCH (Lande et al. 2008), masked hypertension (Lurbe et al. 2005), and prehypertension (Redwine and Daniels 2012; Stabouli et al. 2009; Urbina et al. 2011).

Carotid intima-media thickness (cIMT) measured by high-resolution ultrasound is identified as a morphological change in the arterial wall secondary to elevated BP. Increased cIMT has been reported with increasing systolic BP (Ayer et al. 2009; Urbina et al. 2009). Increased arterial stiffness evidenced by reduced brachial artery distensibility (Whincup et al. 2005), higher pulse-wave velocity (Lurbe et al. 2012), and increased augmentation index (Urbina et al. 2011) has also been reported in children with elevated BP (Flynn et al. 2014). Ambulatory arterial stiffness index (AASI), which correlates with pulse-wave velocity, is calculated as one minus the regression slope of DBP plotted against SBP from ABPM (Flynn et al. 2014). Simonetti et al. have reported that AASI is elevated in hypertensive children and correlates with the duration and the origin of hypertension in childhood (Simonetti et al. 2008). However it is important to note that similar to LVMI data, studies involving large patient cohorts for establishing normative ranges of arterial distensibility, or its inverse (arterial stiffness) in children, are needed (Lurbe et al. 2016). Vascular changes manifesting as narrowing of the small retinal arteries have been reported in children with hypertension (Daniels et al. 1991; Mitchell et al. 2007).

Impaired cognitive function and cerebral vascular reactivity have been reported with pediatric hypertension as evidenced by reports of decreased performance on tests of neurocognitive function (Lande et al. 2003), learning and attention problems (Adams et al. 2010), and impaired vascular reactivity to hypercapnia in untreated hypertensive children (Wong et al. 2011).

Assadi (2008) reported the strength of association between LVH and CRP is comparable to that of microalbuminuria in children and adolescents with primary hypertension. Microalbuminuria has

been reported in children with primary hypertension and not WCH (Seeman et al. 2012) and also in obese and AA (Hanevold et al. 2008; Nguyen et al. 2008). The role of microalbuminuria in assessment of pediatric hypertension is unclear. While, the current European and Canadian guidelines recommend evaluation for microalbuminuria in all hypertensive children (Harris et al. 2016; Lurbe et al. 2016); the new United States guidelines recommend against it (Flynn et al. 2017).

## Conclusions

The increasing diagnosis of primary hypertension in children represents an important shift in our understanding of pediatric hypertension. Primary hypertension is diagnosed in children after negative evaluation for underlying secondary cause. Elevated BP in children is associated with end-organ effects (Harris et al. 2016; Lurbe et al. 2016; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004) (for a detailed discussion, see ► Chap. 39, “Sequelae of Hypertension in Children and Adolescents”). Studies have reported increased prevalence of left ventricular hypertrophy, vascular changes, microalbuminuria, and impaired cognitive function in children with elevated BP (Collins and Alpert 2009; Kupferman et al. 2013). Early identification and management of elevated BP in the pediatric population is important to decrease the risks for end-organ injury and adult-onset cardiovascular disease.

## Cross-References

- [Cognitive and Behavioral Aspects of Childhood Hypertension](#)
- [Diagnostic Evaluation of Pediatric Hypertension](#)
- [Epidemiology of Primary Hypertension in Children](#)
- [Insulin Resistance and Other Mechanisms of Obesity Hypertension](#)
- [Neurohumoral and Autonomic Regulation of Blood Pressure](#)
- [Perinatal Programming of Arterial Pressure](#)

- [Stress and Salt Sensitivity in Childhood Hypertension](#)
- [The Role of Dietary Electrolytes and Childhood Blood Pressure Regulation](#)
- [Vasoactive Factors and Blood Pressure in Children](#)

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## Abstract

Blood pressure is a very important vital sign providing significant information into the health of a child. Sustained elevated readings require further evaluation to determine if a child has primary or secondary hypertension. Secondary forms of hypertension are more common in younger children than in adolescents, and often, in those presenting with very elevated blood pressure readings. After careful clinical evaluation, most causes of secondary hypertension in children are readily identifiable. The causes for secondary hypertension are noted in this chapter and discussed in depth elsewhere in this text. In this chapter, we also discuss the clinical challenge of trying to identify a secondary cause for hypertension in a child or adolescent when none is obvious. Improved methods for predicting secondary hypertension in asymptomatic children are needed to guide cost-effective work-up and

would also reduce the likelihood of missing a treatable cause of hypertension.

## Keywords

Secondary • Hypertension • Renovascular • Parenchymal • Coarctation of aorta • Endocrine

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## Introduction

Measuring blood pressure (BP) is now a standard part of routine health assessment in childhood. Recent reports indicate that in children, the prevalence of hypertension (based on repeated measurements) is about 3.5% and the prevalence of elevated BP is about 3.5%; rates are higher among adolescents and obese children (Hansen et al. 2007; McNiece et al. 2007; Singhal et al. 2007). Despite the well-known variability in serial BP measurements in children, there is substantial evidence that BP measured in childhood predicts future BP; those with BP levels in the higher percentiles of the distribution curve tend to maintain that position over time, indicative of BP tracking (Tirosh et al. 2010; Chen and Wang 2008). Although primary hypertension may occur in childhood, secondary causes of hypertension are more common in children than in adolescents and adults (Singh et al. 2016; Flynn et al. 2012). Secondary forms of hypertension are those with an identifiable medical or medication cause for an increase in BP. While the etiology of secondary hypertension may be readily identifiable in some cases, the challenge occurs when evaluating for a secondary cause of hypertension which is not so obvious. If secondary hypertension is suspected, a stepwise approach should be adopted to identify the cause. It is important to review the patient's diet and medication use for potential acute causes for elevated BP. If concern for secondary hypertension remains, then one should look for clinical clues from further history, physical examination, and laboratory testing. Evaluation of children for secondary causes should be tailored to the child and his or her signs and symptoms. If no clues are available, then other factors that likely predict if the child

has primary or secondary hypertension should be identified (discussed later). This is important as the causes of secondary hypertension are sources of potential morbidity and/or mortality (Patel and Walker 2016; Viera and Neutze 2010).

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## Frequency of Secondary Hypertension in Childhood

Secondary hypertension is more commonly found in young children compared with adolescents and adults. In a study published by Gupta-Malhotra et al., characteristics of children at a tertiary pediatric hypertensive clinic with elevated blood pressure readings were evaluated. Of the 423 children referred, 275 children were diagnosed with hypertension: 43% with primary hypertension and 57% with secondary hypertension. The children with essential hypertension were older, had a strong family history of hypertension, and a lower prevalence of preterm birth (Gupta-Malhotra et al. 2015). This was also shown in a study by Flynn et al., in which children with secondary hypertension were more frequently found to be less than 6 years of age (Flynn et al. 2012). Approximately 70–85% of all children between 0 and <12 years of age and 10–15% of all adolescents 12–18 years will have an identifiable secondary cause for hypertension (Viera and Neutze 2010).

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## Causes of Secondary Hypertension in Children

Children and adolescents with secondary causes for hypertension can be divided into two categories. Patients with clues in the history and physical examination that help with making a diagnosis of secondary hypertension (Tables 1 and 2) (Vidi and Meyers 2013) and patients who are asymptomatic with a normal examination who may not have a readily identifiable secondary cause for hypertension. The major causes of secondary hypertension are outlined below and discussed in detail in other chapters.



**Table 1** Acute/transient secondary causes of hypertension

	Causes	Clues on history and physical exam
1.	Acute glomerulonephritis	Preceding streptococcal infection; tea or coca-cola-colored urine; edema; oliguria; sore throat; skin rash
2.	Acute tubular necrosis	Dehydration; decreased cardiac output; NSAID use
3.	Hemolytic uremic syndrome/ Thrombotic microangiopathy	Bloody diarrhea; pneumonia; bone marrow transplant; use of calcineurin inhibitor; pallor; oliguria/anuria; edema
4.	Obstructive uropathy	Abnormal prenatal US; poor stream of urine; abnormal abdominal musculature; undescended testes
5.	Iatrogenic (volume and medication related)	Infusion of intravenous 0.9% saline; glucocorticoids
6.	Vasculitis	HSP; SLE; SVV; Goodpasture syndrome; AGN
7.	Neurological	Head injury; seizures; altered mental status; increased intracranial pressure; autonomic instability; pain
8.	Orthopedic	Long bone or pelvic fracture; traction
9.	Mediations/Drugs	OTC nasal decongestants containing ephedrine/pseudoephedrine; cocaine and amphetamines; steroids and calcineurin inhibitors

**Table 2** Chronic causes of secondary hypertension

	Causes	Clues on history and physical exam
1.	Neonatal	Prematurity; low birth weight; umbilical artery lines; chronic lung disease; post-ECMO; congenital renal malformations
2.	Coarctation of the aorta	Upper to lower extremity BP gradient >20 mmHg; absent/decreased femoral pulses; systolic ejection murmur
3.	Renovascular	Fever, malaise, signs of claudication; absent femoral pulses; abdominal bruit; features of NF1, TS, William's, Turner, and Alagille syndrome
4.	Renal parenchymal disease	Newborn with antenatal diagnosis of ARPKD or CAKUT; history of chronic kidney disease; recurrent UTI and scarring; patients on dialysis or post-renal transplant patient
5.	Endocrine	Diabetes mellitus and proteinuria; tachycardia, episodic flushing, sweating, palpitations, headache; thyromegaly, exophthalmos, tremors; ambiguous genitalia/virilization, features of Cushing's syndrome-obese, buffalo hump, moon facies, acne, hirsutism, abdominal striae, and myopathy
6.	Pulmonary	Snoring; repeated night time awakenings; daytime somnolence

## Renal Parenchymal Disease

### Acute Postinfectious Glomerulonephritis

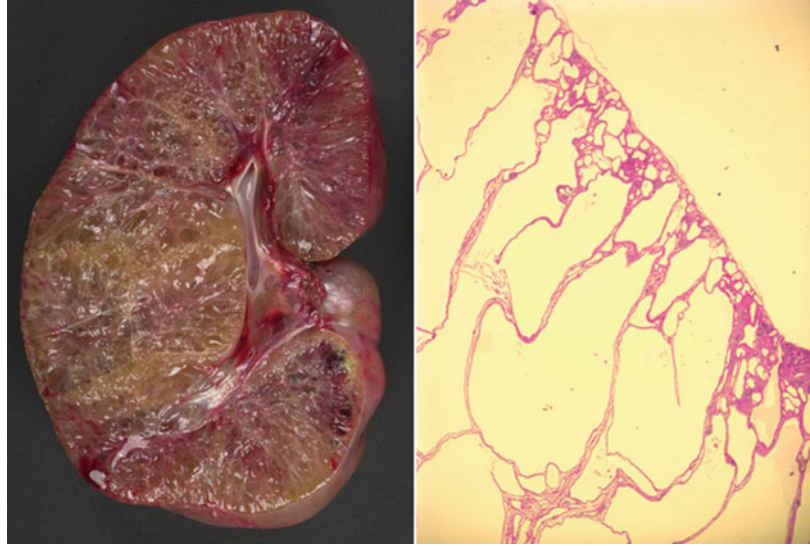
Hypertension in children with acute post-infectious glomerulonephritis (AGN) occurs in 80–90% of cases. Cerebral complications of hypertension occur in approximately 30–35% of children and include headaches, seizures, mental status changes, and visual changes (Eison et al. 2011). Typically there is an abrupt onset of elevated blood pressures in a previously normotensive child, which may be secondary to water and sodium retention, activation of the renin-angiotensin-aldosterone system (RAAS), disturbance of endothelial nitric-oxide balance, or release of endothelin (Nicolaidou et al. 2003).

Initial management should include careful assessment of the patient's volume status for edema and administration of a loop diuretic to augment urine output. Given the underlying etiology of hypertension, diuretics may prove to be especially helpful in BP management with the addition of a long-acting calcium channel blocker (CCB) (e.g., amlodipine) to achieve sustained BP control until there is recovery from the AGN. A sodium-restricted diet is also indicated in BP management.

### Polycystic Kidney Disease

Hypertension is seen in children with autosomal recessive (ARPKD) and autosomal dominant polycystic kidney disease (ADPKD) and is often an initial manifestation present prior to decreased

**Fig. 1 ARPKD and hypertension.** The infant had severe hypertension and pulmonary hypoplasia. The enlarged kidney of 14 cm shows dilated collecting ducts arranged in a radial pattern



renal function (Fig. 1). Antenatal diagnosis, early progression to ESRD, hepatosplenomegaly, bacterial cholangitis, portal hypertension and esophageal varices, and negative family history are all classically seen in ARPKD. Positive family history, extrarenal cysts and cerebral aneurysms, and potentially unilateral renal presentation may be found in ADPKD. Mechanisms of hypertension include intrarenal renin release with ACE and angiotensin II gene upregulation in ARPKD as well as impaired salt and water excretion (Goto et al. 2010). In the neonatal period, use of a loop diuretic and ACE-inhibitor is often required for infants with ARPKD. Use of an ACE-inhibitor or Angiotensin Receptor Blocker (ARB) is recommended for BP control in ADPKD (Reddy and Chapman 2016). The HALT-PKD trial focused on the effects of blood pressure control on total kidney volume and rate of change in eGFR in patients with ADPKD with eGFR > 60 mL/min/1.73 m<sup>2</sup>. They concluded that more rigorous blood pressure control was associated with a slower increase in total kidney volume but no overall change in eGFR (Schrier et al. 2014).

### **Congenital Anomalies of the Kidneys and Urinary Tract (CAKUT)**

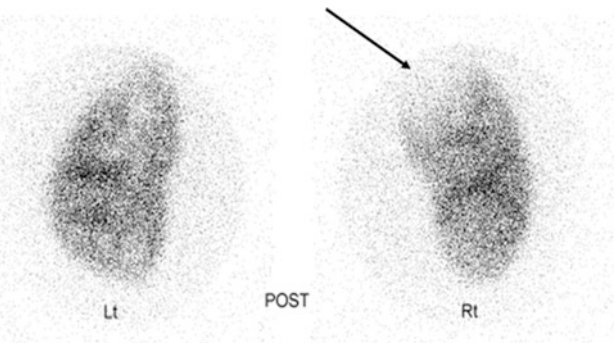
CAKUT comprise a wide range of renal system structural and functional malformations that occur at the level of the kidney (e.g., hypoplasia,

dysplasia, horseshoe kidneys, renal agenesis), collecting system (e.g., hydronephrosis, mega-ureter, unilateral duplex ureter), bladder (e.g., ureterocele, vesicoureteral reflux), or urethra (e.g., posterior urethral valves).

Many of these abnormalities predispose to the development of hypertension (Fig. 2) and cardiovascular disease in adult life; and furthermore, glomerular filtration rate may decrease over time resulting in chronic renal failure (Neild 2009). It has been shown that higher baseline proteinuria and systolic blood pressures are independently associated with chronic kidney disease in this particular subset of patients (Fathallah-Shaykh et al. 2015). Treatment of hypertension using an ACE-inhibitor or an ARB in these patients may improve long-term cardiovascular and renal outcomes.

### **Chronic Kidney Disease**

Most children with chronic kidney disease (CKD) are hypertensive and require pharmacologic therapy for BP control. The prevalence of hypertension increases with decreasing GFR, and hypertension in children with CKD (as in adults) has clinically significant implications for the progression of both renal and cardiovascular disease (Flynn et al. 2008b). Cardiovascular complications in children with CKD include ventricular hypertrophy and carotid artery thickening which are markers for cardiomyopathy and



**Fig. 2 DMSA scan with cortical scarring secondary to vesicoureteric reflux.** A 5-year-old with a previous history of febrile UTI and vesicoureteric reflux. He was noted on routine examination to have stage 1 hypertension.

A dimercaptosuccinic acid (DMSA) scan done as part of the work-up for hypertension shows a right upper pole scar (*arrow*). Blood pressure was controlled with a small dose of an ARB

atherosclerosis. Although supporting data are limited, appropriate treatment of hypertension in children would be expected to ameliorate (at least in part) the long-term poor cardiovascular outcomes in children who develop CKD. The Chronic Kidney Disease in Children (CKiD) study, an ongoing multicenter observational study of North American children with CKD, includes in-office and ambulatory BP measurements in addition to the assessment of cardiovascular structure and function (Furth et al. 2006). Precise longitudinal GFR evaluation will help answer questions about the effect of BP on cardiovascular outcomes and progression of CKD in children (Schwartz and Furth 2007; Barletta et al. 2014; Warady et al. 2015).

Many studies in adults with CKD have demonstrated that ACE-inhibitors and ARBs are the most effective classes of antihypertensive drugs in slowing progression of CKD. This may be secondary to their antiproteinuric effect. Proteinuria is a marker of glomerular injury, but proteinuria in and of itself may further renal tubular injury and promote fibrosis. A prospective multicenter randomized trial in children (ESCAPE) showed that strict mean 24-h BP control (<50th percentile) significantly slows progression of CKD in children, an effect that is independent of ACE-inhibitor use (Wuhl et al. 2009). However, left ventricular modeling and reduction in mass is optimal with ACE-inhibitor use (Matteucci et al. 2013).

Multicenter randomized studies in children have shown the efficacy and safety of using

ARBs for BP control in children and adolescents (Shahinfar et al. 2005; Flynn et al. 2008a). Small, prospective single-center studies demonstrate that ARBs (e.g., losartan, irbesartan, candesartan, valsartan) effectively reduce BP, are antiproteinuric, and slow the progression of CKD in children (Flynn et al. 2008a; von Vigier et al. 2000; Ellis et al. 2004; Simonetti et al. 2006). There may be an additive antiproteinuric effect with combined therapy, but there is also increased risk of hyperkalemia. Diuretics are often required to obtain optimal BP control because of fluid retention with progressive CKD. Thiazide diuretics lower BP well in moderate CKD but are less effective with advanced stages of CKD. Loop diuretics are preferred when the GFR is less than 30 mL/min/1.73 m<sup>2</sup>. Aldosterone receptor antagonists have beneficial effects on reducing cardiac and renal fibrosis, although data in children are limited. The dihydropyridine CCBs (e.g., amlodipine) are also effective in lowering blood pressure in CKD. Used in combination with an ACE-inhibitor or an ARB, the dihydropyridine CCBs do not detract from the benefits of the ACE-inhibitor or ARB in slowing the progression of kidney disease.

### End-Stage Renal Disease: Dialysis

Most children and adolescents undergoing chronic renal replacement therapy are hypertensive. Hypertension can be very difficult to manage in these patients and occurs more frequently with

hemodialysis (HD) than with peritoneal dialysis (PD) (Mitsnefes and Stablein 2005). Control of BP is easier in children on PD.

In a study from the Midwest Pediatric Nephrology Consortium, young age and poor phosphorus control were associated with worse BP control on HD (VanDeVoorde et al. 2007; Kramer et al. 2011). Extracellular volume overload can be managed by prolonging dialysis session times and through additional HD sessions. Reduction of fluid overload may take several weeks, and normalization of BP without the use of medications is possible in some patients. Intensification of HD has improved BP control, whereas conventional dialysis schedules targeting dry weight through increased ultrafiltration tend to be less well tolerated (Hadstein and Schaefer 2008). Use of noninvasive hematocrit monitoring may prevent intradialytic hypotensive episodes (Michael et al. 2004). Sodium modeling and use of lower concentrations of sodium in dialysate during HD also helps reduce BP. Dietary sodium restriction is important in avoiding sodium overload and may reduce intradialytic hypotensive episodes during HD. Adequate volume control during HD, however, may paradoxically increase BP through activation of the RAAS axis (Malik and Raizada 2015). Treatment of this is with an ACE-inhibitor or ARB.

Multiple drug therapy is often required to adequately manage hypertension in children on HD, and interdialytic BP control often remains poor. In euvolemic patients on multiple antihypertensive medications, bilateral native nephrectomy is sometimes required for management of severe refractory hypertension (Power et al. 2001). More detailed information will be provided in ► [Chap. 26, “Hypertension in End-Stage Renal Disease: Dialysis.”](#)

### **End-Stage Renal Disease: Transplantation**

Hypertension is common immediately after renal transplantation. At 1 month after transplantation, approximately 70% of children require antihypertensive medication. This decreases to 50% by 2 years. Hypertension is under diagnosed when ABPM is not used as the standard of care in these children (Hamdani et al. 2016).

The causes of hypertension after transplantation are multifactorial. In the immediate postoperative period, fluid overload and pain contribute to elevated BP. Renin may be secreted from the native kidneys if they are not removed intraoperatively. In addition, pretransplant hypertension and antirejection therapy also contribute to postoperative hypertension. Corticosteroid-induced hypertension occurs through multiple mechanisms including salt and water retention. BP may be significantly reduced after steroid withdrawal (Hocker et al. 2009). Calcineurin inhibitors cause hypertension by inhibiting prostaglandin production and increasing the production of thromboxane. Calcium channel blockers counteract the intrarenal vasoconstriction associated with calcineurin inhibitors. ACE-inhibitors are beneficial through reducing intraglomerular pressure but are typically not started until weeks to months posttransplant to prevent compromise of blood flow to the newly transplanted kidney. Uncontrolled hypertension after transplantation is associated with the development of end-organ damage, including allograft dysfunction, proteinuria, early cardiomyopathy, and premature atherosclerosis. Of note, the presence of metabolic syndrome is strongly associated with left ventricular hypertrophy in these patients (Wilson et al. 2010). Targeted treatment of hypertension after renal transplantation helps delay graft failure and slows development of cardiovascular disease (Mitsnefes 2004). More information on this topic will be provided in ► [Chap. 27, “Hypertension in End-Stage Renal Disease: Transplantation.”](#)

### **Renovascular Disease**

Renovascular disease as an underlying cause of hypertension occurs in about 10% of hypertensive children and less than 5% of hypertensive adolescents. Children and adolescents with renovascular disease usually present with stage 2 hypertension. Clues suggesting renovascular disease in children and adolescents are summarized in Table 2 (Vidi and Meyers 2013). Causes of renovascular hypertension in children are listed in Table 3 (Tullus et al. 2008). Many of these conditions are

**Table 3** Renovascular causes of hypertension in children

Site	Cause
<b>Lumen</b>	Thrombosis
	Tumor invasion
<b>Wall</b>	Fibromuscular dysplasia (FMD)
	Neurofibromatosis I
	Tuberous sclerosis
	Williams syndrome
	Alagille syndrome
	Turner syndrome
	Mid-aortic syndrome
	Vasculitis
	<i>Takayasu's arteritis</i>
	<i>Polyarteritis nodosa</i>
	<i>Kawasaki disease</i>
<i>Other systemic vasculitic</i>	
Radiation	
<b>Extrinsic</b>	Neuroblastoma
	Wilms tumor
	Other tumors
	Retroperitoneal fibrosis
<b>Other</b>	Umbilical artery catheterization
	Trauma
	Transplant renal artery stenosis

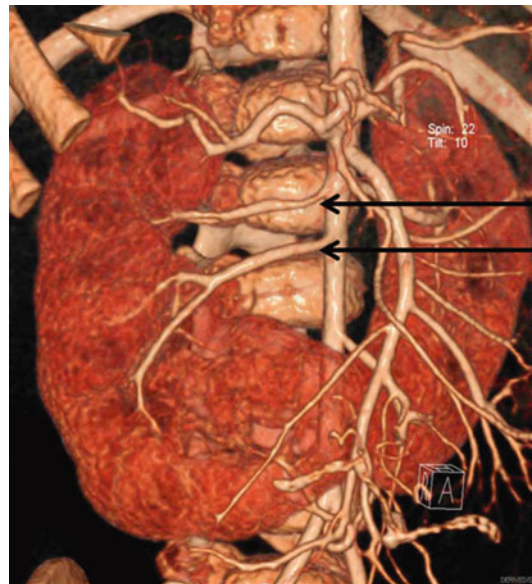
**Fig. 3** Unifocal fibromuscular dysplasia (FMD). Renal angiogram in a 4-year-old child showing tight smooth narrowing of the distal main right renal artery, in keeping with unifocal fibromuscular dysplasia (FMD). Note delayed perfusion and smaller size of the right kidney

discussed in detail in ► [Chap. 28, “Renovascular Hypertension, Vasculitis, and Aortic Coarctation,”](#) here we present a brief overview of renovascular hypertension, vasculitis, and aortic coarctation.

### Fibromuscular Dysplasia (FMD)

FMD is a noninflammatory, nonatherosclerotic arterial disease that most commonly affects the renal and carotid arteries but has been observed in almost every artery in the body. Approximately 60–75% of all FMD cases involve the renal rather than the carotid vessels; the renal predilection, however, may be greater in children than in adults (Green et al. 2016).

The presentation and natural history of FMD in infants and children is quite different from adults. The exact etiology is not known. It is thought to be due to a combination of genetic, hormonal, and mechanical factors. The most prevalent form of FMD identified in children and adolescents is focal FMD which is described by long, irregular, or smooth areas of focal stenosis (Figs. 3 and 4).

**Fig. 4** 3D CTA showing horseshoe kidney with RAS. A 7-year-old girl with Turner syndrome was found to have persistently elevated blood pressure on routine follow-up. Work-up by 3D CTA for the hypertension showed a horseshoe kidney with no obstruction. However, at least 2 of the renal arteries (arrows) to the right renal moiety showed focal tubular stenosis

Persons with FMD may be asymptomatic and only diagnosed at routine medical visits with perhaps an abdominal bruit noted. Children often report nonspecific symptoms including headache, insomnia, fatigue, and chest or abdominal pain (Green et al. 2016). A minority of children with hypertension present with neurological symptoms including seizures, transient ischemic attacks, cerebral infarctions (stroke), subarachnoid hemorrhages, and cranial nerve palsies (Kirton et al. 2013). Presumed FMD can be diagnosed by duplex ultrasonography, magnetic resonance angiography (MRA), and computed tomographic angiography (CTA). The accepted gold standard remains conventional angiography. Treatment involves controlling high blood pressure, re-establishing vascular flow, preventing clotting of the affected vessel(s), and eliminating factors that contribute to further vessel damage (e.g., smoking in teenagers).

### Mid-aortic Syndrome

Although mid-aortic syndrome (MAS) may occur in isolation, there is often involvement of the celiac axis, superior mesenteric artery, and renal arteries. Most cases of MAS are idiopathic, but secondary causes can occur (Onat and Zeren 1969; Sethna et al. 2008). The pathogenesis of idiopathic MAS is speculative and has been attributed to failure of the two dorsal aortas to fuse normally during embryological development (Maycock 1937); rubella infection (Siassi et al. 1970); and abnormal migration of the kidney, as evidenced by the high incidence of multiple renal arteries (Graham et al. 1979). The lesion in idiopathic MAS can be suprarenal, interrenal, infrarenal, or diffuse (Onat and Zeren 1969). Angiography is the gold standard for the diagnosis of idiopathic MAS. However, aortic narrowing can also be demonstrated by CTA, MRA and, occasionally, by abdominal ultrasound and echocardiography. The use of newer 3-D CT technology may reduce the need for invasive angiography (Fig. 5).

Definitive therapy of MAS requires surgical correction and should optimally be delayed until the aorta has reached adult size. Treatment with a multidrug regimen may be necessary until



**Fig. 5 Mid-aortic syndrome with RAS.** A 9-year-old girl was found to have a blood pressure of 150/100 mmHg on routine school screening. Persistence of hypertension led to evaluation by three dimensional computerized tomography (3D CTA). This posterior view shows almost absent perfusion to the left kidney, post stenotic dilatation of a take-off stenosis of the right main renal artery and a 5 cm narrowing in the middle of the descending abdominal aorta consistent with a diagnosis of mid-aortic stenosis (MAS). Additional views showed second order stenosis of the main branch to the upper pole of the right kidney, seen as a perfusion defect here (arrow)

surgical correction can be accomplished, or if surgical correction is not an option.

### Vasculitis

The most common primary vasculitides causing renovascular disease in children are Takayasu's arteritis with Polyarteritis Nodosa (PAN) a distant second. Takayasu's arteritis is a chronic inflammatory disease characterized by giant cell vasculitis involving the aorta and its major branches. It is a rare disease more frequent in Japan, China, Southeast Asia, and parts of Africa (Mathew et al. 2016). Renal angiography is used for diagnosis

which shows stenosis, occlusion, and renal infarcts. Hypertension is found in 33–76% of patients and is usually but not always associated with renal artery stenosis (RAS) (Kerr 1995; Tullus 2015). PAN is a form of necrotizing arteritis of medium-sized muscular arteries with multiple organ involvement. Medium-sized renal vessels are involved which can manifest as loin pain, gross or microscopic hematuria, moderate proteinuria, slowly progressive renal insufficiency, parenchymal infarcts, and severe hypertension.

### Extrinsic Compression and Other Causes

Tumors may cause compression of the renal vasculature causing renin release resulting in hypertension. Renovascular hypertension and obstructive uropathy may occur after treatment of large tumors, in which radiotherapy and post-operative fibrosis may result in RAS or ureteral stricture (Fig. 6) (Koskimies 1982). RAS also develops in 1–2% of pediatric renal transplant recipients (Shokeir et al. 2005; Sozen et al. 2006).

Renal venous thrombosis (RVT) and renal artery thrombosis (RAT) can also result in hypertension. RVT may be due to Protein C, Protein S, Antithrombin III deficiency, Factor V Leiden, and Prothrombin gene mutations or can be acquired

secondary to perinatal asphyxia, maternal diabetes, prematurity, dehydration, infection, nephrotic syndrome, congenital heart disease, and tumors. Perinatal RVT often presents with a triad of gross hematuria, palpable flank mass, and thrombocytopenia. Hypertension develops in about 19% and 22% of those with unilateral and bilateral neonatal RVT, respectively (Lau et al. 2007). Umbilical artery catheter placement in newborns is a risk factor for RAT.

### Management of Renovascular Disease

Management of renovascular hypertension in children requires a multidisciplinary team approach, including a nephrologist, cardiologist, interventional radiologist, and vascular surgeon. Management includes medical treatment of the increased BP, with radiologic and surgical intervention as appropriate (Shroff et al. 2006; Towbin et al. 2007; Ing et al. 1995; Teigen et al. 1992; McLaren and Roebuck 2003). Surgical options, including revascularization or nephrectomy, should be considered when PTA and medical treatment have failed to adequately control the BP. Nephrectomy is appropriate for removing a small, poorly functioning kidney that is driving the hypertension if no benefit is expected after medical or conservative surgical therapy.



**Fig. 6 Obstructive uropathy postradiation therapy.** Shown is severe bilateral hydronephrosis in an 18-year-old with bilateral ureteral stricture that occurred after radiation therapy to treat an infantile rhabdomyosarcoma

### Coarctation of the Aorta

Coarctation of the aorta (CoA) is the fifth most common congenital heart defect, accounting for 6–8% of live births with congenital heart disease, with an estimated incidence of 1 in 2,500 live births. It usually manifests as a discrete constriction of the aortic isthmus. CoA is usually diagnosed in the newborn period or in infants after the ductus arteriosus closes. It is difficult to diagnose in the fetal period due to the presence of the patent ductus arteriosus. It may also be discovered later in childhood and adolescence if the CoA is not severe. It is twice as common in boys compared to girls, and when present in girls one should assess for features of Turner syndrome. Discrete CoA is amenable to potentially curable surgery. Diagnosis is made clinically (e.g., decreased

femoral pulses) and confirmed by echocardiogram; MRA and CTA can be used to define the anatomy of the aorta. Treatment consists of excision of the narrowed segment and end-to-end anastomosis and augmentation of the coarcted aorta using the subclavian artery, the so-called subclavian flap repair (SFR). In older children and adults, balloon angioplasty may be used. Despite successful repair, most patients with CoA have persistent hypertension at rest, during exercise, or both on long-term follow-up. BP control can be achieved in the immediate CoA repair period using an intravenous antihypertensive drug including a beta-blocker (esmolol), CCB (nicardipine), or ACE-inhibitor (enalaprilat) (Nakagawa et al. 2004; Rouine-Rapp et al. 2003). Long-term BP management after CoA repair can be very difficult in children, and there are no prospective studies on the management of these patients. In consideration of the above pathophysiologic mechanisms of persistent hypertension after CoA repair, ACE-inhibitors, ARBs, and CCBs are reasonable choices for initial pharmacologic treatment. The addition of beta-blockers, peripheral alpha-blockers, and diuretics may be required in some patients to achieve a satisfactory BP level. Early surgical intervention reduces the incidence of hypertension on follow-up, but whether or not this merely delays onset is not yet clear. It is conceivable that early “prophylactic” treatment with targeted antihypertensive agents may prevent irreversible changes driving the hypertensive response from occurring and thus improve long-term outlook for these patients. Further research in this area is warranted.

## Medication/Drug-Related Hypertension

### Stimulants for Attention Deficit Hyperactivity Disorder

Medications used to treat attention deficit hyperactivity disorder (ADHD) usually have a modest effect on BP and heart rate. Amphetamines and methylphenidate are sympathomimetics that block the reuptake of norepinephrine and dopamine. Atomoxetine is a nonstimulant medication

that acts as a selective norepinephrine reuptake inhibitor. On average, heart rate increases by 4–6 beats per minute and systolic and diastolic BP increases by 4–6 mmHg; however, some studies have not confirmed any effect on heart rate and BP when compared with placebo (Hammerness et al. 2015). Central-acting alpha-blockers (clonidine, guanfacine) may be used for dual effect to treat ADHD and elevated BP.

### Recreational Drugs

Cocaine produces stimulation of the sympathetic nervous system through inhibition of catecholamine (noradrenalin) reuptake at the synaptic junction causing vasoconstriction. Hypertension associated with cocaine and methamphetamine use is managed by withdrawal of the offending agent. Calcium channel blockers may be used in the treatment of hypertension. In addition, nitroglycerin or nitroprusside have been used in the management of hypertension associated with coronary vasoconstriction.

### Oral Contraceptives

Oral contraceptives can induce hypertension. Contraceptive-associated hypertension is more likely to occur in women with a family history of hypertension (Khaw and Peart 1982). The increase in BP is usually minimal; however, severe hypertensive episodes, including malignant hypertension, have been reported. The main pathophysiologic mechanisms are believed to be an estrogen-mediated stimulation of the RAAS due to increased hepatic synthesis of renin substrate. This results in fluid retention due to increased sodium retention and peripheral vasoconstriction.

### Over-the-Counter Medications

Most nonprescription weight-loss medications contain combinations of an antihistamine and adrenergic agonist (usually phenylpropanolamine, ephedrine, pseudoephedrine, or caffeine). All act by potentiating presynaptic norepinephrine release and by directly activating adrenergic receptors. Alpha-adrenergic intoxication induced by nasal decongestant and cough medications has been reported to result in severe hypertension. Labetalol may be an effective treatment in these



cases. Caffeine can also acutely and transiently increase BP by increasing peripheral resistance. The reaction to caffeine is more pronounced in males than in females and in those with a positive family history of hypertension. Concomitant use of other medications (monoamine oxidase inhibitors, oral contraceptives, and nonsteroidal anti-inflammatory drugs) seems to increase the risk of hypertension (Grossman and Messerli 1995; Harrison et al. 1989).

## Endocrine Causes of Hypertension

### Diabetes

In diabetes types 1 and 2, there are strong associations between glycemic control, BP regulation, and microalbuminuria. The presence of nocturnal hypertension and loss of nocturnal dip in BP seems to herald diabetic complications such as microalbuminuria (Dost et al. 2008; Darcan et al. 2006). In addition to optimization of metabolic control, early diagnosis and prompt treatment of dyslipidemia and hypertension are important in patients with type 1 diabetes (Raile et al. 2007). As in adults, adolescents with type 2 diabetes also exhibit abnormalities of ambulatory BP, dyslipidemia, and microalbuminuria (Ettinger et al. 2005). The main cause of morbidity and mortality in patients with type 1 diabetes is nephropathy, and persistent microalbuminuria is the best marker in adults of the risk of developing nephropathy. Hypertension may also accelerate progression of vascular complications. Management of either form of diabetes includes achieving the best possible glycemic control. Patients who develop microalbuminuria or hypertension should receive treatment with an ACE-inhibitor or ARB. Adult studies suggest that BP goals should be lower in diabetics than in the general population. Because the natural history of microalbuminuria in children and adolescents is still emerging, there is lack of consensus as to when treatment with renoprotective drugs should be initiated in diabetic children (Chiarelli et al. 2002). Routine screening by an endocrinologist for microalbuminuria and early referral to a nephrologist is imperative. More information will be provided

in ► Chap. 22, “Hypertension in Children with Type 2 Diabetes or the Metabolic Syndrome.”

### Thyroid Disease

Hyperthyroidism should be suspected in a hypertensive child with heat intolerance, sweating, palpitations, weight loss despite an increase in appetite, nervousness, hyperactivity, and poor school performance. Signs of hyperthyroidism include tall stature, low body mass index, resting tachycardia, goiter, fine tremor, and exophthalmos. In a series of 106 children with hyperthyroidism, 66% had documented hypertension (Hung et al. 2006). Hypertension can be treated with beta-adrenergic blockers. With appropriate management of the underlying hyperthyroidism, hypertension generally resolves. Fetal and neonatal hyperthyroidism is usually produced by transplacental passage of maternally derived thyroid-stimulating immunoglobulins. Features of hyperthyroidism in the neonate include craniosynostosis, hyperkinesis, eyelid abnormalities, thrombocytopenia, diarrhea, vomiting, failure to thrive, jaundice, hepatosplenomegaly, cardiac failure, arrhythmias, and systemic and pulmonary hypertension. Neonates with hyperthyroidism should be treated with antithyroid drugs, beta-adrenergic blockers, iodine, or iodinated contrast agents, and (as indicated) glucocorticoids or digoxin (Zimmerman 1999). Rarely, nonremitting causes of neonatal hyperthyroidism may require thyroidectomy. There are no prospective studies or case series describing hypertension in children or adolescents with overt hypothyroidism. However, there is a positive relationship between serum thyroid-stimulating hormone levels and hypertension in children and adolescents, suggesting that subclinical hypothyroidism is associated with an increased risk of hypertension.

### Pheochromocytomas and Paragangliomas

Pheochromocytomas and paragangliomas occur rarely during childhood but are more likely to be malignant than in adults. They are often familial and some are related to mutations in succinate dehydrogenase (SDH) gene and genes causing Von Hippel Lindau type 2 (VHL), multiple

endocrinopathy type 2 (MEN2), or neurofibromatosis type 1 (NF1) mutations. Early diagnosis and surgical removal are the most important aspects of therapy for childhood pheochromocytomas. Preoperative, intraoperative, and postoperative medical management is also of crucial importance (Pacak 2007). Adequate preoperative alpha-adrenergic blockade (e.g., phenoxybenzamine, prazosin, terazosin, doxazosin) and beta-adrenergic blockade (e.g., metoprolol, atenolol) are required. To prevent unopposed catecholamine effects, alpha-blockade should be initiated first (usually 10–14 days preoperatively) with beta-blockade starting 2 days later. The combined adrenoceptor antagonists labetalol and carvedilol should not be used as the primary choice for blockade, as the fixed combination of alpha and beta-blockade may paradoxically result in episodes of hypertension and possibly hypertensive crisis. Calcium channel blockers can be used to supplement adrenoceptor blockers for BP control. Calcium channel blockers may also be used to replace adrenoceptor blockers in case of severe adverse effects and to prevent adrenoceptor blocker-induced sustained hypotension. Before surgery, the BP and heart rate should be normalized, and volume should be restored to prevent a surgery-induced catecholamine storm. Metyrosine should also be given as it is an analog of tyrosine that competitively inhibits tyrosine hydroxylase, the rate-limiting step in catecholamine biosynthesis. This drug will partially deplete catecholamine stores, with maximum effect after about 3 days of treatment. In managing biochemically active tumors, metyrosine can be used to help with BP control and improve cardiovascular stability before and during surgery. In addition to the drugs mentioned, volume expansion should be given 6–8 h before surgery. Initial hypotension after surgery may necessitate dopamine and volume support.

### **Cushing's Syndrome/Disease**

Cushing's syndrome in children is due to excessive cortisol-like medications such as prednisone (exogenous) or a tumor that either produces or results in the production of excessive cortisol by the adrenal glands (endogenous). Cushing's

disease results from a pituitary adenoma. Diagnosis is made by clinical features of round face, truncal obesity, acne, and abdominal striae. There can also be delayed growth, virilization, and pseudo-precocious puberty. Diagnosis is confirmed by urine and blood testing of ACTH and cortisol levels following a dexamethasone suppression test. Surgical resection is usually curative but may be very challenging.

### **Congenital Adrenal Hyperplasia**

Congenital adrenal hyperplasia caused by 11-beta hydroxylase and 17-alpha hydroxylase deficiency can cause hypertension. The mechanism is due to decreased cortisone and cortisol production that stimulates the pituitary to produce ACTH and excess of DOC (11-deoxycorticosterone) that has mineralocorticoid effects. Children have ambiguous genitalia and may exhibit virilization.

### **Other**

Other endocrine causes for hypertension include hyperaldosteronism (Conn's syndrome) which is rare in children. The syndrome of apparent mineralocorticoid excess (AME), a genetic disorder, and chronic ingestion of licorice or licorice-like compounds can result in findings similar to those found in Conn's syndrome: hypertension, hypokalemia, metabolic alkalosis, and low plasma renin activity. However, plasma aldosterone levels are low in these disorders, rather than elevated, as seen with Conn's syndrome. Monogenic forms of hypertension including AME, glucocorticoid remediable aldosteronism (GRA), Liddle's and Gordon's syndrome are discussed elsewhere. More information will be provided in ► [Chap. 7, "Monogenic and Polygenic Contributions to Hypertension."](#)

### **Central Causes of Hypertension**

Central nervous system causes for hypertension include raised intracranial pressure secondary to space occupying lesions (tumors, abscess, or hemorrhage), sympathetic nervous system abnormalities, and vasomotor center abnormalities that should be diagnosed prior to treating

hypertension. Patients with postural orthostatic tachycardia syndrome may have elevated blood pressures secondary to increased salt intake encouraged to help in alleviating symptoms. Treatment of hypertension in these patients presents a unique challenge. Nonselective beta-blockers (e.g., propranolol) have been used in low doses for treatment of tachycardia which will also be helpful in blood pressure management (Arnold et al. 2013). Children who have spasticity may be difficult to obtain reliable blood pressure measurements but can have hypertension secondary to autonomic dysreflexia. Centrally acting alpha-blockers can be useful as antihypertensive agents in these patients (Rabchevsky and Kitzman 2011).

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## Miscellaneous Causes of Secondary Hypertension

### Following Orthopedic Procedures

Hypertension in children and adolescents has been described with club foot repair, hip and knee contracture release, traction following pelvic fracture or congenital hip dislocation, immobilization of extremities following casting, and traumatic amputation (Dell and Kaplan 2000; DeVries and Kruse 1998; Heij et al. 1992). The possible mechanisms for orthopedic-associated hypertension include tension on one of the larger nerves of the lower extremities, hypercalcemia, reflex spasm of the renal blood vessels, increased splanchnic sympathetic activity (from soft tissue stretching causing catecholamine release), and salt and water retention secondary to prolonged bed rest. Management includes optimizing pain control, and the use of diuretics and CCBs.

### Environmental Exposures and Hypertension

Mercury/Heavy metals – Exposure of children to any form of mercury can cause a particular syndrome known as acrodynia, or pink disease. This condition is characterized by flushing, itching,

swelling, tachycardia, hypertension, excessive salivation or perspiration, irritability, weakness, morbilliform rashes, and desquamation of the palms and soles. Acrodynia was common among infants in the UK and the US until the late 1940s when it was realized that the condition was primarily caused by exposure to calomel (mercurous chloride) in teething powders and antihelminthic preparations. The combination of an allergic reaction towards mercury with a highly variable individual susceptibility is considered to be important pathogenically. Affected individuals are almost universally infants and small children, and the syndrome develops only in a small proportion of those who are exposed (less than 1%).

Phthalates – Phthalates are environmental chemicals found in daily consumer products and can be classified as either low molecular weight (found in shampoos, lotions, and cosmetics) or high molecular weight (found in flooring, clear food wrap, and intravenous tubing). DEHP (di-2-ethylhexylphthalate) is a high molecular weight phthalate in processed foods found to be associated with increased systolic BP (Trasande et al. 2013).

Cadmium – Cadmium is a toxic metal with high levels of environmental exposure in heavily polluted areas and countries. Even low levels of urinary cadmium have been shown to be associated with hypertension and impaired kidney function (Wu et al. 2016).

Lead – Lead toxicity can cause a variety of nonspecific symptoms including abdominal pain, headaches, poor concentration, and suppressed appetite. Low levels of lead exposure have been associated with higher blood pressures and the development of hypertension (Gambelunghe et al. 2016).

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## Obesity: Primary or Secondary Hypertension?

The prevalence of hypertension is fourfold higher in severely obese children than in nonobese children (Parker et al. 2016). Blood pressure increase in children in the past decade is almost completely attributable to the increased prevalence of obesity

(Sorof and Daniels 2002; Muntner et al. 2004). There is a dose-dependent relationship between the severity of obesity and the risk of hypertension based on BMI, as each 10% increase in BMI is associated with a 3.9 mmHg increase in systolic BP (Dorresteijn et al. 2012). Children who are overweight or obese are at risk for developing primary hypertension. These children also often have a positive family history of obesity and hypertension which increases their risk. They tend to present with mild or stage 1 hypertension.

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### **Sleep-Disordered Breathing and Hypertension**

The etiology of sleep-disordered breathing in children was once thought to be primarily due to adenotonsillar enlargement but is now believed to be due to a combination of neuromuscular, inflammatory, anatomic, and genetic factors. This is evidenced by studies which fail to show any correlation between adenotonsillar size and obstructive sleep apnea (OSA) severity and by studies that show that tonsillectomy and adenoidectomy is not always effective in curing OSA (Marcus 2001). Although studies in children are limited, the pathogenesis of OSA-related cardiovascular disease is thought to be due to interactions between hypoxemia from recurrent obstruction with resultant oxidative stress causing inflammation and endothelial dysfunction (Ryan and Bradley 2005) and increased nocturnal sympathetic activation as a consequence of multiple arousals (in response to obstructive events). There are very few studies which have assessed the effects of tonsillectomy and adenoidectomy in children with OSA and effect on BP and cardiovascular outcome. The results have been variable, showing either a significant reduction in diastolic BP load or an increase of systolic BP with recurrence of OSA, or no change in BP after surgery (Ng et al. 2010; Amin et al. 2008; Apostolidou et al. 2008; Quante et al. 2015). However, additional cardiovascular disturbances including increased sympathetic activity (Constantin et al. 2008) and ventricular dysfunction (Ugur et al. 2008) have shown improvement after tonsillectomy

and adenoidectomy. In summary, it seems that early detection and management of OSA in children may improve BP and reduce later cardiovascular morbidity.

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### **Approach to Asymptomatic Patients with a Normal Physical Examination**

Patients with hypertension may present with symptoms including nausea, emesis, dizziness, mental status changes, blurry vision, nosebleeds, chest pain, seizures, or coma. However, most often, patients with hypertension are asymptomatic. A thorough physical examination, including careful recheck of blood pressure in the upper and lower extremities, is imperative. Physical examination findings that may point to a secondary cause can be subtle and easily missed. The difficulty arises when a detailed history, including family history, medication ingestion, environmental exposure, and dietary intake, is taken and in revealing plus there is a total absence of physical examination findings to guide clinical decision making.

It has been found that the presence of four features: absence of symptoms/signs, normal serum creatinine, positive family history of hypertension, and elevated BMI increase the likelihood of primary hypertension (Gomes et al. 2011). In a report from the Midwest Pediatric Nephrology Consortium among 246 referred patients, there was no difference in age, distribution of weight, or stage II hypertension in those with primary versus secondary hypertension (Kapur et al. 2010). Thus, neither obesity nor mild hypertension excludes the possibility of a secondary cause. It would be useful to have a better way of predicting secondary hypertension in asymptomatic children (Table 4) (Vidi and Meyers 2013). This would help with cost-effective directed work-up and reduce the likelihood of missing a treatable cause of hypertension.

In a study, the daytime systolic BP was higher in 50 adults born prematurely when compared with 30 full-term control adults (Keijzer-Veen et al. 2010). Recent studies show that increased birth weight, rapid postnatal growth and increased

**Table 4** “Likelihood factors” that may help differentiate primary from secondary hypertension in asymptomatic patients with no other clinical or laboratory findings

	Predictors	1 HTN	2 HTN
1.	<b>Age</b>		
	Less than 12 years	–	+
2.	<b>History</b>		
	<i>Prenatal</i>		
	Prematurity	+	+
	Low birth weight	+	+
	<i>School age</i>		
	Advanced postnatal weight gain	+	–
	Maternal smoking	+	–
	<i>Puberty</i>		
	Accelerated skeletal maturation	+	–
	<i>Adolescent</i>		
	Sleep disordered breathing	+	–
	High fructose diet–hyperuricemia	+	–
3.	<b>BP</b>		
	Systolic HTN	+	–
	Diastolic HTN	–	+
4.	<b>Renal ultrasound</b>		
	Renal US: Discrepancy in size of kidneys $\geq 1.5$ cm	–	+

current weight were positive predictors of an increased risk of primary hypertension (Bowers et al. 2011; Hindmarsh et al. 2010; Filler et al. 2011). In a study of 412 adults, 49–51 years of age, in the Newcastle Thousand Families Study, birth weight was a statistically significant predictor of hypertension but was quantitatively much less important than BMI (Mann et al. 2011). Thus, some of the clinical factors associated with primary hypertension include: family history, low birth weight, prematurity, exposure to maternal smoking (Cohen et al. 2010), hyperuricemia which is linked to increased consumption of fructose-containing beverages (Jalal et al. 2010), accelerated skeletal maturation in adolescents independent of BMI (Pludowski et al. 2009; Trachtman and Gipson 2012), and sleep-disordered breathing.

Baracco et al. identified predictors for secondary hypertension including age 5–12 years, elevated diastolic casual BP, and a discrepancy on ultrasound in the size of the kidneys of greater than 1.5 cm (Baracco et al. 2012). They also recommend the following investigations in an

asymptomatic individual in whom a secondary cause for hypertension may be present:

- Baseline basic metabolic panel (as patients may be started on ACE-inhibitors/ARBs and diuretics)
- Urinalysis
- Renal ultrasound looking for any scarring or structural abnormalities including assessing kidney sizes for discrepancy
- Echocardiogram
- Plasma renin activity (PRA) to determine the antihypertensive of choice. If the PRA is low, then use a diuretic for sodium and water retention and if the PRA is elevated then treat with an ACE-inhibitor
- No thyroid studies or urine for catecholamines are recommended unless the patient is symptomatic or the clinical story is suspicious for thyroid dysfunction or pheochromocytoma

Based on the above results and risk factors, we suggest a “likelihood” table to help predict whether an asymptomatic child has primary

hypertension or whether secondary hypertension needs consideration requiring further focused investigation.

In addition, ambulatory blood pressure monitoring can be a useful tool to distinguish between primary and secondary hypertension. Patients with secondary hypertension tend to have daytime diastolic BP elevation and nocturnal systolic BP elevation (Flynn 2002). Reduced nocturnal BP dip has also been found in patients with secondary hypertension on ambulatory blood pressure monitor studies (Seeman et al. 2005).

## Conclusion

The etiology for a secondary cause of hypertension in children is not always obvious. In some children, clues from history and examination will point towards a cause. On the other hand, in asymptomatic children with hypertension, careful consideration needs to be given to the likelihood that a secondary cause for hypertension is present. Subtle clues on history, physical examination, and initial evaluation need to be considered when deciding if further work-up for a potential treatable underlying cause for the hypertension is required in an individual patient. Identification of a secondary cause for hypertension in children permits targeted therapy with greater likelihood of success in adequate blood pressure control.

## Cross-References

- ▶ [Hypertension in Children with Type 2 Diabetes or the Metabolic Syndrome](#)
- ▶ [Hypertension in End-Stage Renal Disease: Dialysis](#)
- ▶ [Hypertension in End-Stage Renal Disease: Transplantation](#)
- ▶ [Insulin Resistance and Other Mechanisms of Obesity Hypertension](#)
- ▶ [Monogenic and Polygenic Contributions to Hypertension](#)
- ▶ [Obesity Hypertension: Clinical Aspects](#)
- ▶ [Renovascular Hypertension, Vasculitis, and Aortic Coarctation](#)

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## Abstract

Hypertension is a common feature of pediatric chronic kidney disease (CKD) and is associated with CKD progression, early markers of cardiovascular disease, and impaired neurocognitive functioning. Prospective research has demonstrated that the prevalence of hypertension in this population is higher than previously thought and that hypertension is frequently underdiagnosed and undertreated. Identifying and treating hypertension in children with CKD require familiarity with the use of pediatric normative blood pressure values and clinical guidelines as well as correct measurement technique. This includes the application of ambulatory blood pressure monitoring (ABPM), which can be helpful in both diagnosis and management. Agents which target the renin-angiotensin-aldosterone system (RAAS) are recommended as first-line therapy to treat hypertension in children with CKD, though multiple medications may be required to achieve sufficient BP control.

## Keywords

Blood pressure • Hypertension • Chronic kidney disease • Child • Adolescent • Cardiovascular

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population. This research has also led to the creation of clinical guidelines with unique BP targets for this population, as well as specific diagnostic and therapeutic recommendations.

**Introduction**

Hypertension contributes substantially to the development of CKD among adults and has been the second-leading cause of end-stage renal disease (ESRD) in the USA for several decades (USRDS 2015). Controlling hypertension is an important factor in slowing the progression of CKD and cardiovascular disease in the adult population (Klag et al. 1996; Peterson et al. 1995; Prospective Studies Collaboration 2002). In contrast to adults with hypertensive kidney disease, children with CKD are far more likely to have hypertension as a consequence of kidney disease, and CKD as a result of chronic hypertension is exceedingly rare. The true prevalence of hypertension among children with CKD, however, has likely been underestimated until recently, as demonstrated by the results of large, multicenter studies. These studies have contributed greatly to our understanding of not only the prevalence but also the consequences of untreated hypertension in this

**Definition of Hypertension in Children with CKD**

Several clinical guidelines on the diagnosis and management of hypertension in children with CKD have been published in the last 10–15 years, with some differences with regard to threshold for treatment initiation and target BP (Table 1) (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004; NKF 2004; Becker and Wheeler 2012; Lurbe et al. 2016). The 4th Task Report, until recently the most widely utilized guideline for diagnosis and management of hypertension in children (including those with CKD), defines hypertension as an average BP  $\geq$ 95th percentile for age, sex, and height percentile on three separate occasions (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). An average BP between the 90 and 95th percentiles is classified as pre-hypertensive. There is no

**Table 1** Summary of clinical guidelines for diagnosis and treatment of hypertension in children with CKD

Guideline (year)	Definition of hypertension	Measurement technique	BP for treatment initiation	Target BP
4th Task Force Report (2004)	>95th percentile	Auscultated	n/a	<90th percentile
KDOQI (2004)	>95th percentile	Auscultated	n/a	<90th percentile or <130/80 mmHg
KDIGO (2012)	Not specified	Auscultated	>90th percentile	$\leq$ 50th percentile
ESH (2016)	$\geq$ 95th percentile or >140/90 if $\geq$ 16 year	Auscultated/ ABPM	n/a	<75th percentile or <130/80 if $\geq$ 16 year Proteinuria: <50th percentile or <125/75 if $\geq$ 16 year <sup>a</sup>

ABPM ambulatory blood pressure monitoring, BP blood pressure, CKD chronic kidney disease, ESH European Society of Hypertension, KDOQI Kidney Disease Outcomes Quality Initiative, KDIGO Kidney Disease Improving Global Outcomes, MAP mean arterial pressure

<sup>a</sup>Includes clinic, home, or ambulatory BP measurements

specific threshold at which medication initiation is recommended, but specific BP targets are provided for children with CKD. The KDOQI guidelines for management of hypertension were published in the same year but are based on prior reference norms (from the 1996 BP working group) (NKF 2004). A definition of hypertension is not specified but treatment targets are suggested. The KDOQI guidelines have largely been replaced by those put forth by KDIGO (Becker and Wheeler 2012). The KDIGO guidelines, meant to serve as a global reference rather than just for the USA (as in the case of KDOQI), incorporate newer evidence in the treatment of hypertension in CKD to specify lower treatment goals. While a definition of hypertension is not specified, the guidelines recommend that treatment be initiated when the auscultated BP is >90th percentile for age/sex/height.

Slightly different recommendations are found in the recent European Society of Hypertension pediatric guideline (Lurbe et al. 2016). These guidelines reflect emerging evidence linking BP targets with intermediate outcomes, such as CKD progression, proteinuria, and other early markers of cardiovascular disease. The definition of hypertension is similar to that in the 4th Task Report ( $\geq 95$ th percentile), with the caveat that for children  $\geq 16$  years old the adult thresholds should be used (130–139/85–89 for high-normal and  $\geq 140/90$  for hypertension). The ESH treatment targets are also lower and differentiate between children with and without proteinuria. The guidelines further recommend the use of ABPM in diagnosing hypertension in certain populations, including children with CKD, as well as in assessing BP control in certain children under treatment. New pediatric BP guidelines for the USA have just been issued (Flynn et al. 2017) and are summarized in the Appendix to this text. Clinicians should review these for changes in guidance related to pediatric patients with CKD.

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### Prevalence of Hypertension Among Children with CKD

Estimates of the prevalence of primary pediatric hypertension in the USA are quite variable, with differences attributed to measurement technique,

setting, and population surveyed. In recent years, the reported prevalence has ranged from 3% to 4% (Din-Dzietham et al. 2007; McNiece et al. 2007; Yang et al. 2016). In the pediatric CKD population, recent studies have confirmed that elevated BP is much more common (Table 2). Early data characterizing hypertension among children with CKD came from the NAPRTCS (North American Pediatric Renal Trials and Collaborative Studies) registry. Based on casual measurements obtained in the clinical setting (including both oscillometric and auscultatory BPs), hypertension was present in 28–41% of 3,861 children with CKD enrolled from 1994 to 2001 (Mitsnefes et al. 2003). Additionally, approximately one-third of the patients with BPs in the normotensive range had been prescribed antihypertensive medications. Combining this information to create a broader definition of hypertension (controlled, normal BP plus medication; uncontrolled, elevated BP plus medication; or undiagnosed, elevated BP and no medication), the overall prevalence was estimated at 67%. Importantly, among the children in this group, less than one-third had controlled BP, suggesting that hypertension was both common and undertreated. While valuable, these data are limited by a lack of standardized BP measurements.

The CKiD (Chronic Kidney Disease in Children) study, a multicenter prospective observational study of children with CKD in North America, has provided a more rigorous characterization of BP in children with CKD. Baseline data using casual BPs (cBP) obtained by auscultation according to standardized procedures were analyzed (Flynn et al. 2008). The definition of hypertension in this analysis, designed to be inclusive, captured patients with elevated BP (>90th percentile), hypertensive BP (>95th percentile), and controlled hypertension (antihypertensive medications, personal history of elevated BP and normal BP). Applying this definition to the 432 children with available baseline study data, 54% were classified as hypertensive. It is important to note that of the hypertensive patients, just under half (47%) had either undiagnosed or uncontrolled hypertension. This group represents one-quarter of the total patients in the study.

Additional information regarding BP status in pediatric CKD comes from a later CKiD analysis

**Table 2** Prevalence of HTN among children with CKD and ESRD

	Study population	Method of BP measurement	Definition of HTN	% hypertensive	% controlled
<b>CKD</b>					
Mitsnefes et al. (2003)	NAPRTCS (n = 3,861)	cBP	BP >95th percentile	28–41% (BP only) 67% (BP and/or meds)	33%
Flynn et al. (2008)	CKiD (n = 432)	cBP	BP >90th percentile +/- meds or history of HTN	54%	53%
Samuels et al. (2012)	CKiD (n = 332)	ABPM	Mean BP ≥95th percentile OR loads ≥25%	52% abnormal ABPM	Not reported
<b>ESRD</b>					
Chavers et al. (2009)	USRDS (n = 624)	cBP	BP >95th percentile or meds	79%	26%
Halbach et al. (2012)	NAPRTCS (n = 3,447)	cBP	BP >95th percentile or meds	81–84%	15–26%
Kramer et al. (2011)	ESPN/ERA-EDTA (n = 1,315)	cBP	BP >95th percentile or meds	68–70%	26–45%
<b>Transplant</b>					
Sorof et al. (1999)	NAPRTCS (n = 4,821)	n/a	Medication use	60%	n/a
Sinha et al. (2012)	Multicenter UK (n = 564)	cBP	BP >95th percentile or meds	56–66%	67%
Seeman et al. (2006)	Single-center Czech Republic (n = 36)	ABPM	BP >95th percentile or meds	89%	47%
Gulhan et al. (2014)	Single-center Turkey (n = 29)	ABPM	BP >95th percentile or meds	93%	18.5%

*ABPM* ambulatory blood pressure monitoring, *BP* blood pressure, *cBP* casual blood pressure, *CKD* chronic kidney disease, *CKiD* Chronic Kidney Disease in Children Study, *ESPN/ERA-EDTA* European Society of Pediatric Nephrology/European Renal Association-European Dialysis and Transplant Association, *ESRD* end-stage renal disease, *HTN* hypertension, *NAPRTCS* North American Pediatric Renal Trials and Cooperative Studies, *UK* United Kingdom, *USRDS* United States Renal Data System

based upon ambulatory BP monitoring (ABPM) data (Samuels et al. 2012). ABPM recordings at 1 year after study entry were available for 332 children. Almost half of the subjects (42%) had a normal recording, consistent with either normotension or controlled hypertension, and a small number had white coat hypertension (4%). Among the children with normal recordings, the majority (~75%) had been prescribed antihypertensive medications. The percentage of study subjects with previously undiagnosed, confirmed hypertension (defined as an elevated casual BP as well as abnormal ABPM recording) was relatively low (15%). A surprising finding was the high prevalence of masked hypertension, defined as a normal casual BP but abnormal ABPM

recording. One hundred sixteen children, or 35% of the study subjects, were in this group, with a significant proportion having abnormal sleep BP. Again, combining these categories to create an inclusive definition of hypertension, subjects with masked hypertension, confirmed hypertension, and controlled hypertension (normal ABPM recording but history of hypertension) comprised nearly two-thirds (73%) of the CKiD study cohort.

It is important to note that the CKiD ABPM study was conducted prior to the publication of updated American Heart Association (AHA) criteria for BP classification on ABPM in children (Flynn et al. 2014). The earlier classification scheme did not specifically address how to

incorporate either diastolic BP or isolated nocturnal hypertension into the diagnosis. In contrast, the CKiD investigators considered an ABPM recording as abnormal if the mean sleeping or awake BP was  $\geq 95$ th percentile or if sleeping or awake BP loads were  $\geq 25\%$ . The rationale for this broader definition of hypertension (to include children who might otherwise be classified as pre-hypertensive) was to account for the fact that children with CKD are at higher cardiovascular risk and their BP treatment goals are lower than in children with primary hypertension (Becker and Wheeler 2012; Kavey et al. 2006; Parekh et al. 2002).

Although it is difficult to draw direct comparisons between the CKiD and NAPRTCS studies due to differing definitions of hypertension and methods of measuring BP, they both illustrate several features of hypertension among children with CKD. First, they confirm that the overall prevalence is high and higher than is commonly appreciated. Second, a considerable portion of children with CKD have undiagnosed hypertension, either due to masked hypertension or unrecognized elevated BP readings. Lastly, even among children with treated hypertension, many remain uncontrolled.

Not surprisingly, the reported prevalence of hypertension is even higher in children with ESRD, either on dialysis or with a kidney transplant. Multiple large studies of the pediatric dialysis population have demonstrated high rates of hypertension and poor BP control, both in the USA and in Europe (Chavers et al. 2009; Halbach et al. 2012; Kramer et al. 2011). In these large registry studies, 70–80% of children meet criteria for hypertension based on reported casual BPs and antihypertensive use. Among those patients on antihypertensive medications, the majority had uncontrolled BPs (52–74%). In the transplant population, reported rates of hypertension vary based on the definition used and method of measuring BP (ABPM or cBP). Estimates range from 60% to 90%, with studies incorporating ABPM reporting the highest prevalence (Gulhan et al. 2014; Seeman et al. 2006; Sinha et al. 2012; Sorof et al. 1999). The use of ABPM has also demonstrated that nocturnal hypertension is

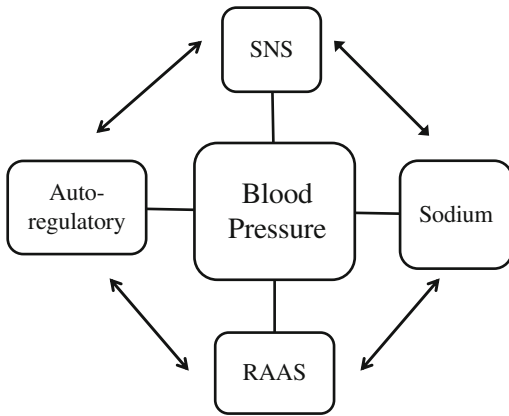
relatively common among pediatric renal transplant recipients (McGlothan et al. 2006). Hypertension in these populations is reviewed in greater detail in ► Chaps. 26, “Hypertension in End-Stage Renal Disease: Dialysis,” and ► 27, “Hypertension in End-Stage Renal Disease: Transplantation.”

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## Pathophysiology

As mentioned above, primary hypertension is rarely the cause of CKD in children (USRDS 2015). Elevated BP, therefore, develops in concert with or as a consequence of the pathophysiology of the underlying kidney disease. For children with congenital abnormalities of the kidneys and urinary tract (CAKUT), the process is gradual and may be subclinical for a period of time. These children were often previously thought to have few issues with high BP and cardiovascular disease until they became oligoanuric, but the application of pediatric ABPM and the ability to detect masked hypertension in these patients have led many to question that assumption (Samuels et al. 2012; Fathallah-Shaykh et al. 2015). Certainly among children with acquired forms of CKD, such as vasculitis or systemic lupus erythematosus (SLE), it is very clear that hypertension develops along with the primary disease.

While there is still much to be learned about the pathophysiologic mechanisms by which hypertension develops in children with CKD, the contributing factors affect BP by altering either cardiac output (CO) or total peripheral resistance (TPR). The two major pathways are volume excess and activation of the renin-angiotensin-aldosterone system (RAAS), but other contributors include autoregulatory mechanisms and the sympathetic nervous system (Fig. 1). It is important to note that these systems, which are discussed briefly below, all interact with one another in complex ways that can involve other organs as well. More in-depth discussion of the pathophysiology of hypertension can be found in ► Chaps. 1, “Neurohumoral and Autonomic Regulation of Blood Pressure,” ► 2, “Vasoactive Factors and Blood Pressure in Children,”



**Fig. 1** Schematic representation of the major categories of factors that influence and regulate blood pressure. The four categories illustrated here contribute independently to blood pressure elevation in CKD, yet there is a considerable amount of cross talk among them. *RAAS* renin-angiotensin-aldosterone system, *SNS* sympathetic nervous system

► 3, “Cardiovascular Influences on Blood Pressure,” ► 4, “Ions and Fluid Dynamics in Hypertension,” and ► 5, “Uric Acid in the Pathogenesis of Hypertension.”

## Sodium

Dietary intake of salt and water leads to volume expansion and a subsequent increase in cardiac output. Under normal physiologic conditions, the increased cardiac output would suppress renin and aldosterone secretion, thereby decreasing sodium recovery in the kidney, allowing for the excretion of the excess salt and water. With decreasing GFR, the mechanisms supporting natriuresis in the kidney are similarly impaired, with salt and water excess contributing to hypertension, which can occur even in the absence of edema. Other factors are involved in the response to salt loading, including eicosanoids and kininogens, as well as cross talk with the sympathetic nervous system (SNS) (DiBona 2003; Koomans et al. 1982; Rhaleb et al. 2011).

The contribution of sodium excess to hypertension in children with CKD is likely variable, being most pronounced in those with advanced

CKD and oliguria and especially in those on dialysis (see ► Chap. 26, “Hypertension in End-Stage Renal Disease: Dialysis”). In children with polyuria, as is commonly seen in young children with CKD secondary to CAKUT, a state of sodium deficit is more frequently observed (Holliday et al. 1967). As will be discussed below, the role of sodium restriction in children with CKD when addressing hypertension should be individualized based on the clinical situation.

## Renin-Angiotensin-Aldosterone System (RAAS)

When afferent arteriolar stretch is reduced in a low-volume state, plasma renin activity is increased, the RAAS is activated, and the end result is increased vasoconstriction through the actions of angiotensin II (ATII). In animal models and adults with CKD, the RAAS is inappropriately activated as GFR declines (Ibrahim and Hostetter 1998; Warren and Ferris 1970). That is, while renin activity may be “normal” in these patients, it may be inappropriate given the degree of positive sodium and fluid balance. The excess secretion of renin is believed to originate in scarred areas of the renal parenchyma or regions that are poorly perfused. By triggering the RAAS, the process of renal fibrosis can continue to induce further injury. In addition to vasoconstriction, ATII also stimulates the SNS, sodium reabsorption, and aldosterone release (Cogan 1990; Kobori et al. 2007). Aldosterone in turn acts via the mineralocorticoid receptor to increase sodium reabsorption in the distal tubule.

## The Sympathetic Nervous System

The SNS is another important contributor to the development of hypertension in patients with CKD. Studies in adults have used both direct (microneurography) and indirect (heart rate variability, BP variability, and baroreceptor response) measurements to assess SNS activity in patients with primary hypertension and CKD and in those on hemodialysis (Barletta et al. 2014; Converse

et al. 1992; Rubinger et al. 2013). These studies have consistently demonstrated SNS activation in the setting of CKD, with an inverse relationship between GFR and SNS activity, and decreased SNS activity with the use of ACE inhibitors (Grassi et al. 2011; Ligtenberg et al. 1999). Proposed mechanisms by which the SNS contributes to hypertension include: afferent nerve signaling from areas of necrosis or fibrosis, decreased nitric oxide (NO) due to increased asymmetric dimethylarginine (ADMA), and other modulating factors, such as genetic differences, oxidative stress, and inflammation (Grassi et al. 2012; Vink and Blankestijn 2012). The cross talk between the SNS and the RAAS appears to be bidirectional in animal studies, where renal nerve stimulation has been shown to increase both renin secretion and sodium reabsorption (DiBona 2003; Kopp and DiBona 1993).

### Autoregulatory Systems

Local factors at the endothelial level include nitric oxide (NO), endothelin-1, and vascular stiffness. NO potentiates vasodilation, and NO-deficient states are associated with hypertension, progression of CKD, and adverse cardiovascular outcomes (Baylis 2012; Reddy et al. 2015). Factors that can reduce NO in CKD include decreased L-arginine availability (substrate for NO synthesis), increased ADMA (a competitive inhibitor for NO synthase) and free radicals, and decreased NO synthase activity (Lin et al. 2013; Baylis 2012). Endothelin-1 (ET-1) is a potent vasoconstrictor produced by vascular endothelial cells that contributes to hypertension, arterial stiffness, and other processes leading to atherosclerosis (Dhaun et al. 2006). Circulating levels of ET-1 are elevated among adults with CKD and represent a potential source of intervention that is currently under study. Vascular stiffness due to calcification of the arterial or arteriolar wall, chronic inflammation, and likely other factors also impairs the ability of local autoregulatory systems to respond appropriately to high volume states (Briet et al. 2012; Townsend and Tomiyama 2013).

### Pharmacologic Factors

Children with CKD are frequently prescribed several classes of medications that can independently cause an increase in BP. Perhaps the most common examples are glucocorticoids. Although previously thought to increase BP primarily by activating the mineralocorticoid receptor and inducing salt and water retention, the mechanisms of glucocorticoid-induced hypertension are not fully understood. Some evidence argues against the principle role of volume expansion and suggests an imbalance in vasoconstriction and vasodilation, as well as RAAS activation (Fardet and Feve 2014). Calcineurin inhibitors (tacrolimus and cyclosporine) can increase BP by both systemic and renal vasoconstriction. Several mechanisms for this have been proposed and demonstrated, including increased SNS activity, endothelin, and ATII and decreased NO (Horne et al. 2012). Lastly, erythropoietin-stimulating agents (ESAs) have been shown to induce hypertension, particularly on initiation. There have been several proposed mechanisms, including remodeling of the arterial wall and alterations in smooth muscle cells, rendering them less responsive to vasodilatory factors, particularly NO (Vaziri 1999). Initially proposed mechanisms related to increased hematocrit have not been consistently supported by later studies (Sasaki et al. 2003).

### Secondary Hyperparathyroidism

The role of secondary hyperparathyroidism in the development of vasculopathy and cardiovascular disease is an area of active research and likely to be complex. In CKD, the decreased production of 1,25(OH)<sub>2</sub>-vitamin D in the setting of reduced renal 1 $\alpha$ -hydroxylase levels induces increased renin production. Additionally, the resulting increase in ATII inhibits klotho expression, which decreases with CKD progression, presumably in concert with FGF-23 resistance (DeBorst et al. 2011). FGF-23 levels in children with CKD are elevated prior to other markers of abnormal mineral metabolism (phosphorus and parathyroid hormone), supporting the concept of



early development of cardiovascular disease (Portale et al. 2014). Klotho deficiency has been associated with multiple features of vasculopathy, including endothelial dysfunction and vascular calcification, and implicated as a risk for cardiovascular mortality (Vervloet et al. 2014).

## Uric Acid

Understanding the contribution of uric acid to the development of primary hypertension has been an area of interest in both children and adults for many years. Proposed mechanisms include RAAS activation, suppression of NO and endothelial cell proliferation, and increased smooth muscle cell proliferation (Wang et al. 2014). Although there are numerous studies documenting an association between elevated serum uric acid and primary hypertension, including several in children and adolescents, a causal relationship is not well established. There are conflicting studies on the relationship between uric acid and hypertension in children with CKD. One single-center study in children with CKD found that elevated uric acid was significantly associated with both hypertension and an eGFR  $<60$  mL/min/1.73 m<sup>2</sup>, but the sample size was relatively small (Noone and Marks 2013). Similarly, data from the CKiD study have shown a positive association between elevated baseline uric acid levels and CKD progression. In contrast to the previous study, however, baseline uric acid was not independently associated with hypertensive status (Rodenbach et al. 2015). Until more prospective data are available, the role of uric acid in the development of CKD-associated hypertension remains unclear.

## Risk Factors for Hypertension Among Children with CKD

There are several patient characteristics associated with a higher risk of hypertension in children with CKD (Table 3). Some of these risk factors are consistent with those related to primary hypertension in both children and adults, such as obesity

**Table 3** Risk factors for hypertension in children with CKD

CKD	Dialysis	Transplant
Age	Age	Immunosuppressive medications
Race	Race	Time since transplant
Obesity	Glomerular disease	
Glomerular disease	Shorter time on dialysis	
Shorter duration of CKD		

CKD chronic kidney disease

and black race (Flynn et al. 2008). Other factors are more specifically connected to CKD. Longer duration of CKD and the presence of glomerular disease (versus non-glomerular disease, such as CAKUT) had a higher risk for both hypertension and uncontrolled BP in the CKiD cohort. Male sex was associated with uncontrolled BP among known hypertensive children but not with hypertension in general. Interestingly, some factors that may be assumed to influence BP status, such as GFR and age, were not significant predictors of either hypertension or controlled BP. Parental history of hypertension and low birth weight, characteristics known to be associated with primary hypertension in the non-CKD population, were also not predictive of hypertension in this cohort.

Proteinuria is an important factor not only associated with CKD progression in children, but BP control as well. When several large adult prospective trials demonstrated that controlling hypertension reduced proteinuria, independent of the anti-proteinuric effects of medications such as ACE inhibitors, many concluded that hypertension was the important influencing factor. In part because of these findings, most adult guidelines recommend lower BP treatment goals for adults with significant proteinuria (Becker and Wheeler 2012; Lurbe et al. 2016). Longitudinal data from the CKiD study, however, have suggested that the relationship between hypertension and proteinuria in the progression of CKD may be more complex. The presence of proteinuria was predictive of poorer BP control over time in the study cohort, even though the mean SBP decreased in the

study cohort as a whole (Kogon et al. 2014). The investigators suggested that proteinuria may alter vascular physiology thus making hypertension more difficult to treat in such patients. A separate analysis of the contributions of BP and proteinuria to CKD progression among children with non-glomerular disease showed both to be independent risk factors. Among children with normal BP, proteinuria contributed to a faster rate of GFR decline, while among children with elevated BP, GFR declined at all levels of proteinuria, suggesting that these two variables may not necessarily be additive in this population (Fatallah-Shaykh et al. 2015). These findings demonstrate that there is more to be learned about the relationship between proteinuria and BP in children with CKD.

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## Diagnosis

### Measurement Methods

Measuring BP in children in the clinical setting presents several challenges and factors to consider. Firstly, access to the appropriate equipment is extremely important to obtain reliable readings. A range of cuff sizes should be available, from infant to large adult and thigh cuff, and the correct one selected based on the mid-arm circumference (Gomez-Marin et al. 1992). As with standard recommendations for BP measurements in adults, the child should be calmly resting in a seated position with foot support for several minutes prior to cuff inflation, and the arm should be supported at approximately the level of the heart. Auscultatory measurements are preferred and considered the gold standard method of BP measurement in pediatric CKD (Flynn et al. 2012). By auscultation, the first Korotkoff sound denotes systolic BP and the fifth sound diastolic BP. Often the 5th Korotkoff sound can be heard all the way to zero mmHg; in such cases the 4th Korotkoff sound should be used to estimate diastolic BP or BP remeasured with less pressure applied over the brachial artery (excessive pressure over the brachial artery has been associated with loss of K5).

Although auscultation is recommended, oscillometric devices may be more commonly

available in some settings, including those used in the home setting. The principal disadvantage to these devices is that they indirectly estimate BP, and readings may not correspond to those obtained by auscultation (Park et al. 2001). Oscillometric devices measure mean arterial pressure (MAP) and through proprietary algorithms that differ by manufacturer, calculate systolic and diastolic BP. There are a few advantages to oscillometric devices, including consistent repeated measurements, elimination of bias, and ease of use (Butani and Morgenstern 2003). They may also be the only way to obtain BP readings in infants and very young children, as it can be extremely difficult to measure BP by auscultation in this age group.

### Ambulatory Blood Pressure Monitoring (ABPM)

As ABPM devices have become more commonly available for use in children, they are becoming part of the standard evaluation for children with elevated BP. This is particularly pertinent to children with CKD who, as mentioned above, have a relatively high prevalence of both nocturnal and masked hypertension. As with casual BP measurements, dedicated pediatric equipment is necessary, with care taken to apply the appropriate cuff size prior to test initiation. Education of both parent and child is important, and a diary should be kept with sleep and wake times along with periods of activity and timing of medications. One limitation of ABPM is the need for the child to be able to cooperate with the test, which generally occurs around age 6–8 years. Children with developmental delays or other neurocognitive impairments may not tolerate wearing the ABPM device at any age.

As mentioned above, modified consensus guidelines on the interpretation of ABPM were recently updated (Table 4) (Flynn et al. 2014). At the present time, ABPM criteria for the diagnosis of hypertension do not differentiate between children at higher or lower cardiovascular risk, including children with CKD. Research is ongoing, however, and many analyses from the CKiD

**Table 4** Revised classification for interpreting ABPM in children

	Office BP	Mean ambulatory SBP or DBP <sup>a</sup>	SBP or DBP load, % <sup>a</sup>
Normal	<90th percentile	<95th percentile	<25
White coat hypertension	≥95th percentile	<95th percentile	<25
Pre-hypertension	≥90th percentile or >120/80	<95th percentile	≥25
Masked hypertension	<95th percentile	>95th percentile	≥25
Ambulatory hypertension	>95th percentile	>95th percentile	25–50
Severe ambulatory hypertension	>95th percentile	>95th percentile	>50

Adapted from Flynn et al. (2014)

ABPM ambulatory blood pressure monitoring, BP blood pressure, SBP systolic blood pressure, DBP diastolic blood pressure

<sup>a</sup>Applies to either sleep or wake period (or both)

study propose more conservative criteria for hypertension in this population. Further details on ABPM methodology and application to patient management can be found in ► [Chaps. 16, “Ambulatory Blood Pressure Monitoring Methodology and Norms in Children,”](#) and ► [41, “The Role of ABPM in Evaluation of Hypertensive Target-Organ Damage.”](#)

## Home BP Monitoring

While it is commonly accepted that out-of-office BP readings are often lower than those obtained in the clinical setting, the role of home or self-BP monitoring is not well established in children. Until recently, there were no published guidelines for the use of home BP monitoring in the pediatric population, though it has commonly been utilized by pediatric nephrologists for many years (Woroniecki and Flynn 2005). Based on several pediatric studies either focused on or incorporating home BP (HBP) readings, the 2016 ESH guidelines provide suggested standards for use of HBP (Table 5). In areas where ABPM is not available, home BP (HBP) monitoring may be a cost-effective, acceptable alternative. Ease of use, availability of standard pediatric equipment, and ability to obtain readings over a longer period of time are potential advantages. Additionally, HBP monitoring can provide out-of-

**Table 5** Recommendations for home BP monitoring

Measured daily for at least 3–4, but preferably 7, consecutive days
Twice-daily readings (morning and evening)
Child should be seated in a quiet room, resting with back and arm support for at least 5 min prior to measurement
Two measurements per occasion, taken 1–2 min apart
Home BP is the average of the above readings, with those taken the first day discarded

Adapted from Lurbe et al. (2016)

BP blood pressure

office BP readings in those children who will not tolerate ABPM, either due to age or developmental concerns.

There are several drawbacks, however. First, despite studies showing that HBP correlates relatively well with ABPM and presence of target organ damage, there are no accepted standards for use in terms of timing, number or readings or normative values (Furusawa et al. 2009; Salgado et al. 2011; Stergiou et al. 2009; Wuhl et al. 2004). In fact, the only large study comparing HBP and office BP readings, the Arsakeion school study, found that the difference between office BP and HBP changed with age (Stergiou et al. 2015). This study of 778 school-age children contains the only published data on HBP norms in the pediatric population. The cost of providing monitors is another potential drawback. In the USA, most insurance carriers do not provide coverage for

durable medical goods, and the financial burden for purchase often falls on the patient and family. Lastly, it is important to note that pediatric experience with home BP monitors is limited to those devices using the brachial artery, and among those few have been validated in the pediatric population. Radial/wrist monitors and devices that have not been validated in children are not recommended.

## Normative Values

The most frequently used normative values for casual BP in children are elaborated in the *4th Report* and are derived from data on over 63,000 healthy children in the USA from ages 1–17 years, including the National Health and Nutrition Examination Survey (NHANES) (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). It is important to note that NHANES specifically seeks to oversample minority racial groups in the USA, so the diversity of this reference population makes the normative values applicable to a wide range of patient groups. Importantly for children with CKD, who may have growth impairment due to their underlying disease, the values in the 4th Report cover a range of height percentiles for age and sex.

The reference values used for ABPM interpretation are less robust than those for casual BP. Due to the more resource-intensive nature of performing ABPM, obtaining such large, population-level sample sizes is not practicable. The best available data, and those currently recommended by consensus guidelines, are derived from a population of predominantly Caucasian children from Central Europe (Flynn et al. 2014; Soergel et al. 1997; Wuhl et al. 2002). In addition to a lack of patient ethnic diversity, the data on diastolic BP norms have long been considered problematic. Despite the knowledge that both systolic and diastolic BP vary with age and height, the survey data in this reference group resulted in very little differences in diastolic BP norms for a very wide range of heights. Finally, and importantly for children with

CKD, it has been noted that the study population included very few children who were shorter (<140 cm), so the reference data in this range may not be as strong (Flynn 2011).

## Additional Testing

Hypertensive target organ damage in children is less common and often subtler than that found in adults. In cases of severe elevations in BP, children can have seizures, hypertensive encephalopathy, and cardiac dysfunction (Baracco and Mattoo 2014). Although cardiovascular disease remains the leading cause of death among adults with CKD, death and other cardiovascular events, such as myocardial infarction and stroke, are rare in children, even among those with longstanding CKD. Research efforts in the pediatric CKD population have focused on identifying early and intermediate markers of cardiovascular disease. The hope is to better understand the pathophysiology of developing cardiovascular disease and identify important clinical markers and/or possible areas of intervention. The majority of these markers, including carotid intima-media thickness, pulse wave velocity, and altered cardiac function, are still primarily used as research tools and have not yet been adopted for clinical use (Brady et al. 2012; Lindblad et al. 2013; Shroff et al. 2013; Urbina 2016).

Echocardiography, by contrast, is widely available clinically and can be used to evaluate the presence of both left ventricular hypertrophy (LVH) and elevated left ventricular mass index (LVMI) (Daniels et al. 1998; Hanevold et al. 2004). Clinical guidelines currently recommend that echocardiograms should be performed on all children with confirmed hypertension. The information obtained on echocardiogram should include both a subjective assessment of ventricular function and size and also accurate measurements of LMVI by experienced technicians. Interpretation of the LVMI in children should be done with pediatric reference values, with an LVMI >95th percentile for age and sex considered elevated (Khoury et al. 2009).

## Treatment

### Goals of Therapy

As mentioned above, there are several clinical practice guidelines specifying BP treatment goals for children with CKD (Table 1). The earliest among these, and likely the most commonly used, is the 4th Task Force Report, published in 2004 (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). Although the 4th Report does not comment on a BP level for treatment initiation among children with CKD, it recommends a BP target of <90th percentile in this population. These guidelines have just been updated (Flynn et al. 2017); see the Appendix for a summary. Blood pressure guidelines from the Kidney Disease Outcomes Quality Initiative (K/DOQI) were also issued in 2004 and specify similar treatment goals: BP should be <90th percentile or <130/80, whichever is lower (NKF 2004). Both of these guidelines are based partly on extrapolated data from adult evidence-based guidelines for the treatment of hypertension, specifically the JNC-7 report (Chobanian et al. 2003).

The Kidney Disease Improving Global Outcomes (KDIGO) initiative published hypertension guidelines for children with CKD in 2012 (Becker and Wheeler 2012). In a departure from all prior guidelines, where no BP threshold is specified for starting pharmacologic therapy, the authors recommend initiating antihypertensive treatment when the BP is >90th percentile in children with CKD. Additionally, treatment goals in these guidelines are more aggressive, recommending that casual BP be lowered to less than the 50th percentile, unless achieving this target is precluded by symptoms of hypotension. It is important to note that this recommendation receives a grade of “low” quality of evidence, given that it is based on a single trial (ESCAPE) and a single observational study (CKiD data). It is also complicated by the fact that the ESCAPE results were based upon ABPM, whereas the recommendation itself specifies a casual BP target.

Clinical trial evidence provided from the ESCAPE study led to the publication of updated

guidelines by the European Society of Hypertension (ESH) in 2009 and again in 2016 (ESCAPE 2009; Lurbe et al. 2009, 2016). The ESCAPE study was a randomized controlled trial in children with CKD undergoing treatment with a fixed dose of ramipril. Participants were assigned to either conventional BP control (MAP by ABPM at the 50–90th percentile) or “intense” BP control (MAP by ABPM <50th percentile). Providers could administer additional agents not targeting the RAAS to achieve target BP. The investigators found that those in the intensified arm of the study had slower rates of CKD progression compared to those in the conventional treatment arm, particularly in cases of proteinuria. In part because of these findings, the ESH guidelines continue to recommend that, among children with CKD, SBP and DBP should be targeted to less than the 50th percentile by ABPM in those children with proteinuria and less than the 75th percentile in those without proteinuria. These percentiles apply to all modalities of BP measurement (home, office, and ABPM) (Lurbe et al. 2016).

It is encouraging to see the publication of more studies in children with CKD and hypertension, including one large clinical trial, and the inclusion of children in CKD clinical guidelines over the past 10–15 years. Despite these advances, it is important to note the variability among the current guidelines with regard to thresholds for treatment and BP targets. These differences are largely due to a paucity of evidence and are based on expert opinion in some cases. Indeed, large clinical trials in adults designed to identify the optimal threshold BP to slow CKD progression have not yielded a definitive answer to date. Additionally, there has been a recent focus on BP measures beyond office readings, including parameters of ABPM, pulse pressure, and noninvasive measurements of central BP, and how they relate to clinical outcomes (Cha et al. 2013; Gabbai et al. 2012; Gorostidi et al. 2013). Some evidence suggests these measures may be more accurate prognostic indicators for such outcomes as cerebrovascular events, cardiovascular events, and CKD progression (Fedecostante et al. 2014; Yano et al. 2013). These findings highlight that more research is needed in the pediatric population to identify the

optimal BP target that will minimize CKD progression and future cardiovascular disease risk.

### Non-pharmacologic Measures

In children and adults with primary hypertension, non-pharmacologic interventions are typically recommended as an adjunct therapy to medications (Chobanian et al. 2003). Termed “therapeutic lifestyle changes” in the 4th Report, these interventions include increased physical activity, weight loss, and a low-sodium diet (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). In children with hypertension secondary to CKD, such measures may not always be appropriate. While the prevalence of obesity among children with CKD is higher than previously thought, it is much lower than in the general pediatric population and may not be a primary contributor to elevated BP (Wilson et al. 2011). Similarly, some children with CKD secondary to dysplasia and/or obstructive nephropathy may be polyuric, with both salt and water wasting. Sodium excess is likely not a primary driver of hypertension in these patients, and dietary sodium restriction should be considered carefully in conjunction with a nutritionist to ensure the child’s growth is not impacted (Parekh et al. 2001). It is important to note that the relative contribution to BP reduction from non-pharmacologic interventions (such as increased physical activity or a specific total daily sodium intake) in children with CKD is unknown. Currently the recommendation would be to implement such changes on a case-by-case basis and as the clinical situation indicates.

### Medication Selection

Until the early twenty-first century, there were few antihypertensive medications whose safety and efficacy had been studied in the pediatric population. Passage of the Food and Drug Administration Modernization Act (1997) and Best Pharmaceuticals for Children Act (2002) in the USA provided incentives to close this gap. Although

mostly focused on the newer classes of medications, studies have since generated enough data to permit approval and labeling for pediatric use of most classes of antihypertensive medications (Ferguson and Flynn 2014). Comparative prospective trials demonstrating superiority of one particular class of agent over another and studies on fixed-dose combination pills are still lacking, however.

Current clinical guidelines recommend treating with a single agent to maximum dose and then adding additional agents if BP control has not been achieved (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004; Lurbe et al. 2016). Based on physiologic mechanism and available data from both clinical trials and observational studies, agents that act on the RAAS (ACE inhibitors and angiotensin receptor blockers) are currently recommended as first-line therapy for hypertension in children with CKD (Ferguson and Flynn 2014; Gartenmann et al. 2003). This approach is supported by data from the CKiD study, demonstrating that children receiving RAAS agents had better BP control than those prescribed with other classes of antihypertensives (Flynn et al. 2008). Prospective analyses of CKiD data evaluating the effect of proteinuria on GFR decline have also shown that both degrees of proteinuria and hypertension are independent risk factors for more rapid decline (Fathallah-Skaykh et al. 2015; Warady et al. 2015). For this reason, RAAS agents should certainly be considered first-line antihypertensive agents among children with CKD and proteinuria. The side effect profile of RAAS agents is generally favorable, but patients should be counseled appropriately regarding teratogenicity and risk for volume depletion in certain circumstances. Periodic monitoring of potassium and renal function is also recommended.

Additional agents may be required to achieve adequate BP control, and selection is typically guided by clinical considerations. Evidence-based information is now available for children on dosing, safety, and efficacy for most classes of antihypertensive medications, and most have been shown to be equally effective at lowering

BP. Dual therapy with both ARB and ACE inhibitor may have additive effects on both BP and proteinuria, but safety concerns with this combination in adults preclude making this a standard approach in children (ONTARGET 2008). In addition to their BP-lowering effects, beta-blockers have been found to have both antirenin and anti-proteinuric effects in adults and also target the SNS, which has been implicated as a mechanism of hypertension in CKD (Wright et al. 2003). These agents should not be used in children with reactive airway disease and diabetes, and many require dose adjustment for lower GFR. In patients with a component of volume overload, diuretics can be a helpful addition as second-line agents. Those with significant proteinuria or reduced GFR may require higher doses to achieve an appropriate clinical response, and loop diuretics are likely to be more effective than thiazides. Beta-blockers and diuretics in general should be avoided in children and adolescents who are competitive athletes.

Dihydropyridine calcium-channel blockers (DHP CCBs) were commonly prescribed as first-line therapy for children with CKD in the past, but their lack of a clear anti-proteinuric effect makes them less desirable as monotherapy for many of these patients (Robles et al. 2016). They may be beneficial in certain patients for whom RAAS agents are not tolerated and are certainly useful as secondary agents. Other classes of antihypertensive medications that have been used successfully in children include direct vasodilators, such as hydralazine or minoxidil, and central alpha-agonists. Aliskiren, a direct renin inhibitor, has been shown to be effective at lowering BP in adults and in one small pediatric study (Sullivan et al. 2013). In the pediatric trial, results are available for an extension study with follow-up to 1 year, but have not yet been published. However, clinical use of aliskiren is currently somewhat limited as adult trials have found a significant incidence of worsening renal function, hypotension, and hyperkalemia in patients with CKD (Harel et al. 2012). A continued extension of the pediatric trial to look at neurocognitive and growth outcomes in children treated with aliskiren is ongoing.

In summary, current available evidence in children with CKD supports the use of RAAS agents as first-line therapy for the treatment of hypertension. If additional agents are needed to achieve adequate BP control, beta-blockers, CCBs, and/or diuretics should all be considered. Expanding medication choice to other classes of antihypertensives may be needed based on the clinical situation.

## Medication Dosing

As evidence for the safety and efficacy of medications used to treat the sequela of CKD in the pediatric population has increased, the impact of taking multiple medications on adherence and quality of life should also be considered. Along with antihypertensive medications, children with advanced CKD may be prescribed medications to treat anemia, bone disease, and growth delays, and the overall pill burden can be quite high. Analysis of factors impacting medication adherence among participants in the CKiD study has shown that frequency of dosing appears to be more important than the absolute number of medications (Blydt-Hansen et al. 2014). Therefore, it would seem reasonable to preferentially choose antihypertensive medications with a once-daily dosing schedule when clinically feasible.

## Chronotherapy

Among adults with CKD, studies have suggested that nocturnal hypertension more closely correlates with adverse cardiovascular outcomes compared to daytime hypertension (Hermida et al. 2011). Chronotherapy is the practice of timing antihypertensive medication dosing with an aim to restore the physiologic circadian variation in BP and reduce cardiovascular risk. While studies conducted in adult patients with primary hypertension have suggested a benefit to such an approach, the data among adults with CKD is less robust, and no studies have been done in the pediatric CKD population. A recent systematic review of seven trials in the adult CKD population

concluded that bedtime dosing of at least one antihypertensive medication should be considered in adults with CKD, but no conclusions could be made about specific classes of medications or stage of CKD, and only two studies included cardiovascular outcomes in addition to changes in BP (Liu et al. 2014). Although it seems reasonable to consider bedtime dosing of antihypertensive medications in children with CKD, additional research is certainly needed.

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## Sequelae of Hypertension in Pediatric CKD

### CKD Progression

The association between hypertension and CKD progression has been well established in adults, through both observational and interventional studies (Klag et al. 1996; Peterson et al. 1995). As mentioned previously, hypertension as a primary cause of CKD in children is extremely rare. Among children with established CKD, however, it appears to be a major contributor to progression. Early data examining this relationship comes from one of the few multicenter trials in the pediatric CKD population (Wingen et al. 1997). The trial was designed to test the effects of a low-protein versus conventional diet on CKD progression over a period of 2–3 years, while simultaneously examining other factors, including BP. The 284 enrolled patients from 25 centers were ages 2–18 with stages 3–4 CKD. At the conclusion of the trial, protein restriction had no adverse effects on growth but also did not affect glomerular filtration rate (GFR) decline. In a multivariate analysis, only hypertension (defined as SBP >120 mmHg) and proteinuria (24-h urine protein >50 mg/kg) were found to independently correlate with GFR decline. Although this study was not designed to determine causality between these factors and CKD progression, the results were among the first to suggest a key role for BP.

At least two large retrospective studies using data from the NAPTRCS registry have confirmed hypertension to be an independent risk factor for CKD progression in children (Mitsnefes et al.

2003; Staples et al. 2010). Mitsnefes et al. found that, among those children in the registry with a starting eGFR (estimated GFR) between 50 and 75 mL/min/1.73 m<sup>2</sup>, hypertensive children progressed significantly faster to the study endpoint (either renal replacement therapy or a decline in eGFR by 10 mL/min/1.73 m<sup>2</sup>) than normotensive children. A multivariate analysis also found systolic hypertension to be an independent risk factor for GFR decline, along with African-American race, glomerular disease, and older age. This association was confirmed by a later analysis of 4,166 children in the NAPTRCS registry with CKD stages II–IV and a small, single-center, retrospective study from Poland (Ksiazek et al. 2013; Staples et al. 2010).

Prospective data examining the impact of hypertension on CKD progression is also provided by the CKiD study. Although the study is ongoing, data examining longitudinal changes in GFR over a 1-year period from study enrollment suggest that annualized GFR decline is faster among patients with an abnormal ABPM compared to those with a normal ABPM, though the relationship was not statistically significant (Samuels et al. 2012). Among children in the study with non-glomerular disease or rapid disease progression (defined as a decrease in GFR by 50% or renal replacement therapy over a 1-year period), BP was an independent risk factor for GFR decline (Fatallah-Shaykh et al. 2015; Warady et al. 2015). Based on these findings, it is clear that appropriate treatment of hypertension remains one of the few interventions available to slow progression of CKD in children.

### Left Ventricular Hypertrophy (LVH)

LVH is an important risk factor for cardiovascular morbidity and mortality in adults and is not uncommon among children with CKD. Young adults diagnosed with CKD and ESRD during childhood have a dramatically elevated mortality rate compared to the general population, with the majority of deaths due to cardiovascular disease (Parekh et al. 2002). Reported rates of LVH in children with mild to moderate CKD (stages 2–4)



range from approximately 20–50%, with some variation due to methodology and definition of LVH (Johnstone et al. 1996; Matteucci et al. 2006; Mitsnefes et al. 2010; Simpson et al. 2010; Sinha et al. 2011). Early studies examining the relationship between BP and LVH did not find a significant association between BP and increased left ventricular mass index (LVMI) or abnormal cardiac geometry. Other factors, such as GFR, sex, age, and evidence of anemia or inflammation, were instead found to be significant predictors of LVH (Johnstone et al. 1996; Matteucci et al. 2006). Other studies have contradicted these findings. Data from 49 children with non-hypertensive CKD at a single center found 33% had LVH on echocardiogram. The authors also found a positive association between LVMI and systolic BP, even within the “normal” range (Sinha et al. 2011). A cross-sectional analysis from the CKiD study used both echocardiographic and ABPM data to evaluate predictors of LVH. The authors found that both confirmed (OR 4.3) and masked (OR 4.1) hypertension were the strongest independent predictors of LVH and that GFR was not significant (Mitsnefes et al. 2010).

Two prospective studies have provided further information on how BP may be related to LVH in children with CKD. The ESCAPE trial, a randomized, multicenter trial that compared intensive (<50<sup>th</sup> percentile) versus conventional (<90<sup>th</sup> percentile) BP goals during treatment with ramipril, collected echocardiographic data at baseline, 1 year and 2 years on 84 patients (Matteucci et al. 2013). The overall prevalence of LVH decreased from 38% to 25% for the entire study cohort, and LVMI decreased among those patients who had LVH at baseline, but not in patients without LVH. Treatment to intensive BP goals did not have an effect on LVMI, but was significantly associated with improved systolic function, suggesting an independent drug effect on cardiac remodeling. Longitudinal data from the CKiD study looking at the effects of BP on LVMI and LVH also showed that the prevalence of LVH decreased over time (Kupferman et al. 2014). Significant predictors of LVMI included SBP,

anemia, and use of non-RAAS antihypertensive agents. These studies collectively suggest that BP plays a role in the development/regression of LVH in pediatric CKD.

The methodology to most accurately quantify left ventricular mass (LVM) is also an area of active research. The above CKiD study found that female sex was an independent predictor of LVH (defined as LVMI  $\geq$ 95th percentile for age and sex) but not LVMI. This finding was surprising given that other cardiovascular risk factors were generally more favorable among girls than boys in the CKiD cohort. One proposed explanation for this finding is that gender differences in lean body mass (LBM) between girls and boys are more important in assessing LVMI than using age, height, or weight. Reference data for assessment of LVMI based on estimated LBM (eLBM) were recently published (Foster et al. 2016). Additional research applying these criteria to children with CKD will be important in further characterizing the relationship between BP and LVH/LVMI.

### **Carotid Intima-Media Thickness (cIMT)**

To evaluate the development and presence of atherosclerosis, an established risk factor for cardiovascular disease in adults, intermediate markers of vasculopathy have been examined in children with CKD. These include arterial calcification, intima-media thickness (IMT), and measures of arterial stiffness. Both single-center and multicenter studies have shown that children with CKD have increased cIMT compared to healthy controls (Brady et al. 2012; Litwin et al. 2008; Mitsnefes et al. 2005). cIMT worsens over time with advancing stages of CKD, with children on dialysis having the highest measurements (Litwin et al. 2008; Mitsnefes et al. 2005). At least one study has demonstrated regression of cIMT after kidney transplant (Litwin et al. 2008). In the CKiD cohort, both hypertension and dyslipidemia were independent predictors of elevated cIMT, whereas markers of calcium and phosphorus metabolism were not (Brady et al. 2012).

## Other Markers of Cardiovascular Dysfunction

Low heart rate variability (HRV) has been reported in adult patients with ESRD and is associated with an increased risk of cardiac death (Fukuta et al. 2003). Increased BP variability (BPV), a risk factor for adverse cardiovascular and cerebrovascular outcomes in hypertensive patients, has also been reported in the adult CKD population (Gorostidi et al. 2015; Tanner et al. 2015). Using ABPM data from the CKiD study, investigators have demonstrated that among children with CKD, those with hypertension have increased BPV and decreased HRV compared to those with normal BP (Barletta et al. 2014). This analysis was limited to untreated children to remove any potential influence of antihypertensive medications. Replicating these associations in children with CKD suggests that multiple aspects of cardiovascular risk are developing early in these patients.

## Neurocognitive Function

While evidence of neurocognitive deficits among adults with mild hypertension compared to normal controls was identified over 25 years ago, it is only recently that similar studies have been conducted in children with elevated BP. An analysis from the NHANES III survey demonstrated that children with elevated BP (defined as BP  $\geq$  90th percentile) had decreased performance on several cognitive measures compared to those with normal BP (Lande et al. 2003). A series of smaller studies looked at changes after treatment with antihypertensive medications in children with primary hypertension. The investigators found that hypertensive children scored lower on parental reports of executive function and higher on measures of “internalizing” behaviors (such as depression and anxiety) compared to healthy controls (Lande et al. 2009). After 1 year, parent ratings of executive functioning improved (as did BP) in the hypertensive children, but

there was no significant change for the control group, suggesting that elevated BP could have subtle neurologic target organ changes (Lande et al. 2010).

Extensive neurocognitive testing is also a component of the CKiD study to further explore this aspect of CKD in children (Hooper et al. 2011; Lande et al. 2011). Although the overall mean baseline test scores were in the normal range, a substantial proportion of participants scored at least one SD below the mean on several of the tests, including intelligence quotient (IQ) and executive functioning. Higher GFR appeared to be protective on tests of executive functioning, and elevated BP was independently associated with a lower IQ score. Greater visit-to-visit systolic BPV was also found to correlate with lower (worse) scores on a test of executive functioning (Lande et al. 2016). Although these studies are not definitive, they suggest that elevated BP can have early and subtle effects on neurocognitive functioning in children. While the long-term neurocognitive effects of CKD and hypertension are unknown, these early findings again suggest that controlling elevated BP is an intervention that may be beneficial from a neurologic standpoint. Additional research in this area will be important as the life expectancy of patients with childhood-onset CKD continues to improve.

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## Conclusion

Prospective research in the pediatric CKD population has greatly advanced our knowledge of the prevalence, risk factors, complications, and treatment of hypertension among children with CKD. The application of newer clinical and research techniques has enhanced our ability to detect evidence of early cardiovascular disease in this population, and more studies investigating the effects of antihypertensive medications in children have been published. The consistently high prevalence rates endorse the practice of prioritizing the detection and treatment of elevated BP when caring for children with CKD.

Future research should focus on correlating specific treatment goals with clinical outcomes and enhancing our knowledge of optimal use of pharmacotherapy.

## Cross-References

- ▶ [Ambulatory Blood Pressure Monitoring Methodology and Norms in Children](#)
- ▶ [Cardiovascular Influences on Blood Pressure](#)
- ▶ [Endothelial Dysfunction and Vascular Remodeling in Hypertension](#)
- ▶ [Hypertension in End-Stage Renal Disease: Dialysis](#)
- ▶ [Hypertension in End-Stage Renal Disease: Transplantation](#)
- ▶ [Ions and Fluid Dynamics in Hypertension](#)
- ▶ [Methodology and Applicability of Home Blood Pressure Monitoring in Children and Adolescents](#)
- ▶ [Neurohumoral and Autonomic Regulation of Blood Pressure](#)
- ▶ [Uric Acid in the Pathogenesis of Hypertension](#)
- ▶ [Vasoactive Factors and Blood Pressure in Children](#)

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Franz Schaefer

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## Abstract

Hypertension and left ventricular hypertrophy are highly prevalent in the pediatric dialysis population. Ambulatory or home blood pressure monitoring is required to obtain prognostically relevant information about a patient's blood pressure status. Volume status is the primary determinant of blood pressure in dialysis patients; the clinical relevance of additional pathogenic mechanisms such as sympathetic hyperactivity is controversial. The most important measure to maintain normal blood pressure is achievement of the dry weight, which can be facilitated by the use of bioimpedance analysis and intradialytic blood volume monitoring. Dietary salt restriction and avoidance of net salt uptake during dialysis is key to maintain fluid balance. Extended hemodialysis schedules efficiently normalize blood pressure and reverse left ventricular hypertrophy in patients who cannot maintain fluid balance under standard thrice weekly hemodialysis. Pharmacotherapy of hypertension should only be reserved to patients with persistent hypertension despite adequate volume status. The preferable first-line antihypertensive drug class is currently unclear; head-to-head comparative trials are urgently needed.

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## Keywords

Left ventricular hypertrophy • ABPM • Blood volume monitoring

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## Introduction

Young adults with childhood-onset end-stage renal disease (ESRD) suffer from accelerated cardiovascular morbidity (Mitsnefes 2012). Their risk to die of cardiovascular complications is increased up to 1000-fold compared to the age matched general population (Mitsnefes et al. 2013).

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Early cardiovascular lesions are already detectable at childhood and adolescent age and advance as CKD progresses (Schaefer et al. 2017).

While the pathogenesis of this condition is multifactorial, arterial hypertension is the most consistent risk factor associated with structural and functional changes of the heart and large arteries. The myocardium responds to elevated blood pressure in an adaptive hypertrophic process which, if persistent, becomes maladaptive leading to myocardial fibrosis and systolic and diastolic dysfunction. In addition to cardiac changes, persistent hypertension induces intermediate vascular abnormalities such as increased intima media thickness and arterial stiffness. While these changes are typically most severe in children undergoing chronic dialysis, they are potentially modifiable by consequent blood pressure control.

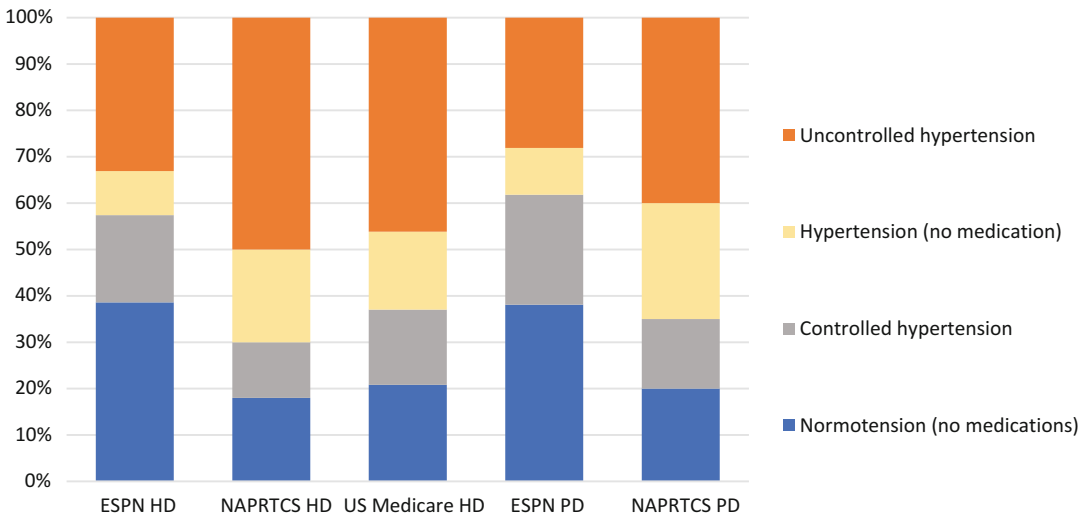
This chapter discusses the epidemiology, etiology, and management of dialysis-associated hypertension. Pediatric data are reported and discussed wherever available; reference to adult dialysis experience and trial evidence is made where specific pediatric information is lacking.

## Epidemiology

### Hypertension

Large registry analyses have demonstrated a high prevalence of hypertension in the pediatric dialysis population (see Fig. 1). A survey of more than 1,300 pediatric dialysis patients from 15 European countries reported to the population-based ESPN-ERA-EDTA Registry disclosed uncontrolled hypertension in 45.5% of children undergoing chronic hemodialysis (HD) and in 35.5% of those treated with chronic peritoneal dialysis (CPD), with a total (controlled or uncontrolled) hypertension rate of 69.7% in HD and 68.2% in CPD (Kramer et al. 2011).

Among 3,447 dialyzed children in the North American Pediatric Renal Trials and Cooperative Studies (NAPRTCS) Registry, uncontrolled or untreated hypertension was found in 67.9% of patients six months after initiation of dialysis and 57.8% were prescribed antihypertensive medications (Halbach et al. 2012). A study of all pediatric long-term hemodialysis patients in the USA showed a hypertension prevalence of 79%; 62% of patients received antihypertensive medications, three quarters of whom still had



**Fig. 1** Blood pressure control in pediatric patients undergoing chronic hemo- (HD) or peritoneal dialysis (PD). Information based on casual blood pressure measurements reported to European (ESPN/ERA-EDTA Registry, Kramer

et al. 2011) and North American registries (NAPRTCS Registry, Halbach et al. 2012; Medicare & Medicaid, Chavers et al. 2009)

uncontrolled hypertension (Chavers et al. 2009). Of note, the information available from these registries is based on reported casual BP. The rate of patients with misclassified blood pressure status due to white coat or masked hypertension may be substantial: assessment of a pediatric dialysis cohort by ambulatory blood pressure monitoring (ABPM) led to reclassification of blood pressure status in one third of patients (Lingens et al. 1995).

Both the European and the North American registries identified young age and hemodialysis treatment modality as a risk factor for higher blood pressure. Furthermore, the underlying renal diagnosis seems to affect the risk of hypertension on dialysis: congenital anomalies of the kidneys and urinary tract were associated with lower blood pressures in the European survey and glomerular diseases with higher blood pressure in the NAPRTCS Registry.

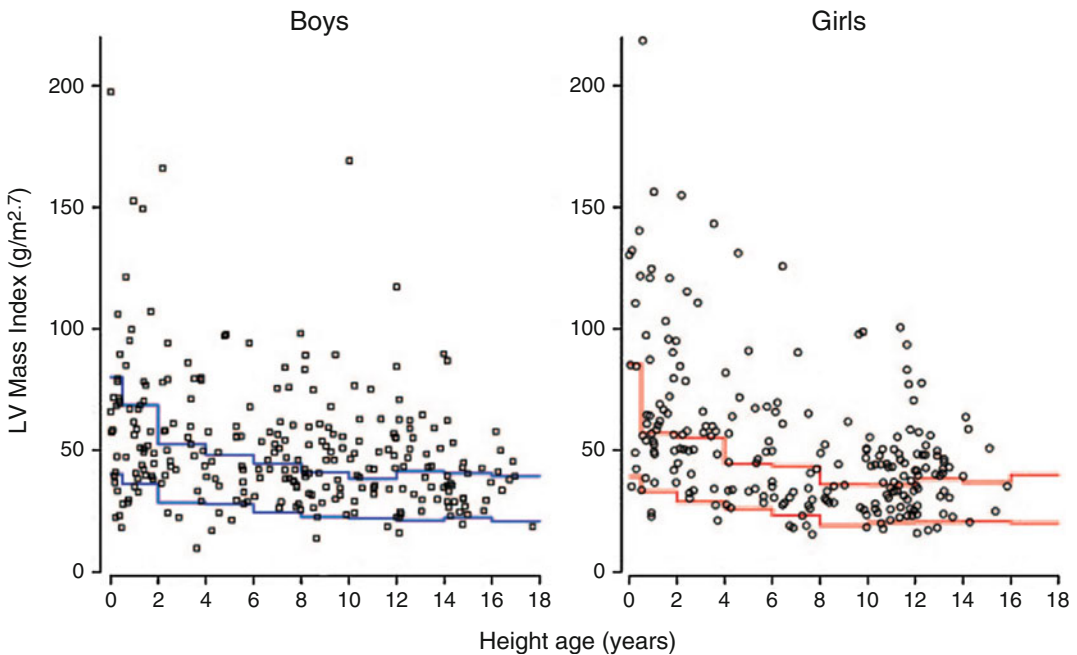
### Left Ventricular Hypertrophy

In end-stage renal disease left ventricular mass is considered an integral measure of the medium-

term impact of blood pressure, anemia, volume expansion, and the fibrogenic effects of the uremic condition. Hence, left ventricular hypertrophy (LVH) is both an intermediate endpoint and an independent risk factor for adverse cardiovascular outcomes.

LVH is highly prevalent in dialyzed children. Echocardiographic studies showed (mainly concentric) LVH in 80% of *hemodialyzed* children, commensurate with the prevalence of hypertension in this population (Mitsnefes et al. 2006; Scavarda et al. 2014). This prevalence is not dissimilar from that observed in adult patients starting hemodialysis (Foley et al. 1995).

Among 507 children undergoing *chronic PD* followed in the registry of the International Pediatric Dialysis Network (IPPN), LVH was present in 48% (Bakkaloglu et al. 2011); LV geometry was concentric in two thirds and eccentric in one third of the patients with LVH. Another 27% of the children exhibited concentric LV remodeling with still normal LV mass. The distribution of LV mass in another IPPN study showed that many children on CPD had elevated LV mass for height age (Borzych et al. 2011; see Fig. 2).



**Fig. 2** Distribution of LVMI for height age in 274 boys and 233 girls. Lines indicate the 10th and 95th percentiles

of LVMI distribution in healthy children, From Borzych et al. (2011)

Almost 30% of patients with initially normal LV mass developed *de novo* LVH within 12 months whereas LV mass regressed to the normal range in 40% of the patients who started PD with LVH, confirming on a larger scale an earlier longitudinal study in 29 incident pediatric dialysis patients, 14 of whom showed a further increase and 15 a regression of LV mass on dialysis (Mitsnefes et al. 2001). While hypertension was the most relevant risk factor for LVH risk in the IPPN study, obesity and hyperparathyroidism were additional risk factors and the diagnosis of renal hypo/dysplasia was associated with a reduced LVH risk.

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## Etiology and Pathogenesis

The mechanisms leading to hypertension in chronic kidney disease are elaborated in detail in the preceding chapter. In children and adults with end-stage renal disease, *sodium and water retention* due to insufficient removal by residual diuresis and dialysis is considered by far the most important hypertensiogenic factor. Hypertensive children on dialysis have lower residual urine output than their normotensive peers, reflecting the frequent failure to compensate diminishing urine output by increased dialytic fluid and sodium removal (Tkaczyk et al. 2006). Strict enforcement of dry weight and normalization of sodium balance normalizes blood pressure without the need for pharmacological antihypertensive therapy (Bakris et al. 2016).

On the other hand, clinical observations such as the moderate correlation of interdialytic weight gain and blood pressure in HD patients (Lingens et al. 1995; Sorof et al. 1999) and the significant decrease in blood pressure following bilateral nephrectomy (Zazgornik et al. 1998) point to additional, volume-independent mechanisms contributing to hypertension in ESRD. There is evidence for increased *peripheral vascular resistance*, which is believed to be driven by sympathetic hyperactivity (Converse et al. 1992; Augustyniak et al. 2002), inappropriate activation of the renin-angiotensin-aldosterone system (RAAS) (Wauters et al. 1981), and deficient

endothelium-dependent vasodilation (Jourde-Chiche et al. 2011). The hyperactivation of the adrenergic system is believed to result from afferent signals arising in the failing kidney. Renal denervation attenuates sympathetic activity and improves hypertension both in models of renal failure and in dialysis patients (Pietilä-Effati et al. 2016). In addition, the RAAS apparently fails to be inactivated, as would be appropriate in a hypervolemic state. The infusion of normal saline fails to suppress plasma renin activity in patients with end-stage renal disease (Warren and Ferris 1970). Notably, treatment with ACE inhibitors normalizes sympathetic activity, suggesting a role of the intrarenal angiotensin tone on afferent neural signaling (Klein et al. 2003). The most important vasodilatory factor secreted by the endothelium is nitric oxide (NO), the absence of which causes severe hypertension. NO production is decreased in CKD (Schmidt et al. 1999a, b). In dialysis patients, the circulating concentrations of asymmetric dimethylarginine (ADMA), a potent NOS inhibitor, are increased five- to tenfold due to accumulation (Anderstam et al. 1997; Schmidt et al. 1999a). ADMA independently predicts mortality and cardiovascular events in patients with ESRD; however, ADMA levels do not correlate with blood pressure (Anderstam et al. 1997).

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## Diagnostic Evaluation

While the procedural guidelines for measuring blood pressure in healthy children also apply to children on chronic peritoneal dialysis (CPD), special considerations must be made regarding the blood pressure measurements in patients undergoing chronic hemodialysis. The default use of the right arm is usually not appropriate for safety reasons when an arteriovenous fistula is in place on this side. Most importantly, however, the absence of a steady state of hydration with treatment-induced fluctuations of blood pressure both during and between the dialysis sessions has substantial implications concerning the required timing and frequency of blood pressure monitoring.

## Peridialytic Blood Pressure Monitoring

A meta-analysis of studies in adult HD patients revealed that blood pressure measurements taken immediately before or after a hemodialysis session provide poor estimates of the interdialytic blood pressure as assessed by 44h ABPM (Agarwal et al. 2006c). Low or absent correlations of peridialytic and interdialytic blood pressures were also observed in pediatric hemodialysis patients (Sorof 1999; Chaudhuri et al. 2011).

The diagnostic performance of peridialytic BP could not be improved by strict standardization of measurements (Rahman et al. 2002) or by averaging several peridialytic BP recordings (Agarwal and Lewis 2001). In addition, peridialytic blood pressures are poorly correlated with target organ damage in adults and children (Agarwal et al. 2006b; Chaudhuri et al. 2011) and are not predictive of cardiovascular mortality (Alborzi et al. 2007).

## Interdialytic Blood Pressure Monitoring

*Interdialytic ABPM* is considered the gold standard approach to BP monitoring in hemodialysis patients. ABPM findings are superior not only to peridialytic but also to home BP monitoring in predicting target organ damage and mortality (Agarwal 2010; Amar et al. 2000). In contrast to the poor prognostic significance of peridialytic BP, interdialytic BP monitoring, performed either by manual BP measurement at home or by ABPM covering the 44h interdialytic interval, yields information that is indicative of end-organ damage such as LV hypertrophy both in adults (Agarwal et al. 2006b) and children (Chaudhuri et al. 2011). Moreover, the mean blood pressure levels observed with ABPM or home BP monitoring are predictive of all-cause and cardiovascular mortality in adults (Alborzi et al. 2007; Agarwal 2010). Mortality is in direct linear relationship with mean interdialytic BP, whereas a U-shaped association with mortality has been suggested for peridialytic BP (Bansal et al. 2015).

The superior information content of ABPM is not only explained by the large number of BP measurements since the better correlation with outcomes persists even when a small number of randomly selected measurements are used (Agarwal et al. 2008). It is more likely that the superiority of ABPM relates to the recording of BP during sleep. An attenuated or absent nocturnal BP decrease (“nondipping”) is very common in HD patients and nondipping is an independent risk factor for cardiovascular mortality both in the general and in the HD population (Amar et al. 2000; Fan et al. 2010).

While ambulatory blood pressure monitoring is also recommended for CPD patients, published ABPM studies in this population are scarce. The first pediatric study comparing ABPM findings in pediatric HD (n = 18) and CPD patients (n = 17) noted higher overall BP but more pronounced nocturnal BP dipping in children on CPD (Lingens et al. 1995). A multicenter study of 47 Turkish children on CPD reported better correlations of ABPM than casual BP with LVMI. Daytime systolic BP load was the most closely associated predictor of LVH (Bircan et al. 2010), with systolic BP load <15% having the best negative predictive value. A study comparing 18 adult patients undergoing Automated PD (APD) and 26 on CAPD found no differences in 24h BP control and circadian BP variation between these treatment modalities and confirmed the association of LVMI with daytime systolic BP load (Jang et al. 2011).

Notwithstanding its prognostic relevance, the use of ABPM in the routine monitoring of blood pressure control is limited by logistic challenges and patient acceptability. Regular *home BP monitoring* may offer a more feasible alternative. A comparative study in adult HD patients demonstrated 80% sensitivity and 84% specificity of home BP monitoring in diagnosing hypertension using 44h interdialytic ABPM as a reference standard (Agarwal et al. 2006a). Also, changes in home BP correlated quite well with changes in ABPM during dry weight probing interventions (Agarwal et al. 2009). Unfortunately the adherence to frequent home BP measurements tends to be low, particularly among patients with poor

fluid compliance who are at highest risk for interdialytic hypertension. In the foreseeable future, the use of mobile health applications may facilitate home BP monitoring. Another challenge is the absence of pediatric reference values for home BP. Whereas well established pediatric reference values are available for ABPM, the distribution of home BP has not been established in healthy children.

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## Nonpharmacological Management

Notwithstanding the evidence for additional volume-unrelated mechanisms contributing to hypertension in dialysis patients, it should be emphasized that fluid overload represents by far the most important etiology for elevated blood pressure in this population. Hence, non-pharmacological measures aimed to remove excess sodium and restore fluid balance are usually more effective in accomplishing blood pressure control than pharmacological interventions. Intense pharmacological treatment in volume-expanded patients can even impede the attainment of the appropriate “dry weight” leading to an apparently paradoxical association of poor blood pressure control with the use of multiple antihypertensive drugs (Agarwal and Lewis 2001).

The degree of fluid excess is almost always underestimated in dialyzed children. Uremic anorexia and catabolism may cause losses of fat and lean mass which are replaced by fluid expansion, resulting in little or no net change in body weight. The sensitive diagnosis of such changes requires watchful clinical assessment and the regular use of supportive technologies such as bioimpedance analysis (BIA) and intradialytic blood volume monitoring (BVM). Mono-frequency BIA provides a relatively precise estimate of total body water in children (Wühl et al. 1996), and multifrequency bioimpedance spectroscopy may even allow to differentiate extracellular fluid volume and lean body mass (Vujčić et al. 2013). BIA sensitively detects subclinical changes of hydration status in children (Zaloszyc et al. 2013). In adult hemodialysis patients, BIA-guided therapy has been associated with improved blood

pressure control, reduced target organ damage, and even superior patient survival (Moissl et al. 2013; Onofriescu et al. 2014).

Intradialytic blood volume monitoring is another technological innovation with potential to improve dry weight adjustment and blood pressure control. Prospective studies in adults and children demonstrated improved 44h ambulatory blood pressure following introduction of the technique (Patel et al. 2007; Candan et al. 2009; Sinha et al. 2011). Sonographic assessment of the diameter of the inferior vena cava provides information on the intravascular fluid status before and after dialysis but is of limited value in determining dry weight (Krause et al. 2001).

Arterial hypertension is closely associated with low serum albumin and EPO resistant anemia in dialyzed children, pointing to volume expansion as a common underlying factor (van Stralen et al. 2012; Borzych-Duzalka et al. 2013) and providing a rationale to consider changes in serum albumin and hemoglobin together with those of weight, BIA, and (in hemodialysis) BVM in the diagnosis and monitoring of hypertension in dialyzed children.

The most important measure to achieve dry weight is the *restriction of dietary sodium intake*. Lowering dietary sodium intake decreases thirst and interdialytic weight gain, leads to improved BP control (Maduell and Navarro 2000), and results in greater improvement of LV mass and function than the routine use of antihypertensive agents (Kayikcioglu et al. 2009).

The majority of children progressing to end-stage renal disease suffer from some form of renal dysplasia; most dysplastic kidney diseases cause salt losing nephropathies and require liberal salt and fluid intake even in advanced CKD. Once residual GFR declines below a certain threshold, dietary salt requirements rapidly diminish and restricted intake becomes necessary. It is important not to miss this turning point, for which rising blood pressure is a sensitive indicator. Given the tight physiologic regulation of serum osmolality, restricting only fluid intake without simultaneously making provisions for limited salt ingestion is futile and not recommended.

In patients undergoing hemodialysis, the concentration of *sodium in the dialysis bath* is a critical determinant of sodium balance. Most hemodialysis units use a default dialysate sodium concentration of 140 mmol/L to preserve intradialytic hemodynamic stability. At this exposure level many patients experience a net sodium gain during dialysis, resulting in a vicious cycle of increased interdialytic thirst and weight gain and ultimately elevated risk of intradialytic hypotension due to large ultrafiltration needs. Dialysis protocols using Individualized dialysate sodium concentrations have demonstrated reduced interdialytic weight gain and improved blood pressure control at an inconsistently increased risk of intradialytic hypotension in adults (reviewed in Georgianos and Agarwal 2016). Sodium profiling, i.e., modifying dialysate sodium concentration during the hemodialysis session, has been associated with better dialysis tolerability in a pediatric study (Sadowski et al. 1993). However, sodium profiling usually leads to a net sodium influx and increased interdialytic weight gain and blood pressure in randomized controlled trials (Song et al. 2005). The same effects have been observed with bolus administration of hypertonic saline, the routine use of which should be avoided.

Another critical factor in hemodialysis is the *weekly cumulative time on dialysis*. Multiple randomized clinical trials in adults have provided evidence that the achievement of blood pressure control is greatly facilitated with intensified hemodialysis regimens, including the use of longer (>4 h) or more frequent (>thrice weekly) dialysis sessions (Bakris et al. 2016). In the Frequent Hemodialysis Network (FHN) trial, the average predialysis systolic blood pressure was reduced by more than 7 mmHg with both short-daily and long-nocturnal dialysis arm relative to standard thrice weekly sessions. Antihypertensive medication use was reduced with both intensified dialysis modalities. Very similar findings were made in pediatric case series of intensified hemodialysis. Normalization of blood pressure and left ventricular mass was observed both with short daily (Fischbach et al. 2004; Goldstein et al. 2008) and with extended nocturnal dialysis schedules (Thumfart et al. 2015).

In *patients undergoing CPD*, blood pressure control depends on the efficacy of sodium and water removal. In general, convective sodium and water removal can be enhanced by use of automated peritoneal dialysis (APD) as compared to continuous ambulatory peritoneal dialysis (CAPD) schedules. In an interesting single-center study from Mexico, 310 children were switched from CAPD to APD when the technique became available. Daily ultrafiltration increased by more than 40%, and the fraction of patients requiring antihypertensive medications decreased from 83% to 38% (Fabian Velasco et al. 2008). The use of the APD modality was found protective from LVH in 507 CPD children followed in the IPPN Registry (Bakkaloglu et al. 2011).

However, the use of APD to maximize convective salt and water removal requires careful attention to peritoneal transport physiology and assessment of individual transport properties. Very short cycles with high dextrose concentrations increase the relative contribution of aquaporin channels to ultrafiltration, i.e., selective water removal with sodium retention (“sodium sieving”), resulting in thirst and increased fluid turnover. Also, the individual peritoneal transporter characteristics should be assessed by standardized peritoneal equilibration testing (PET) to identify patients with rapid dialysate glucose resorption (“high transporters”), who are at risk of poor ultrafiltration, fluid overload, hypertension, and LVH (Correa Rotter and Cueto-Manzano 2001). Ideally, the patient’s PD prescription should be tailored according to the transporter category. Recently, a novel APD prescription approach with sequential short- and longer-dwell exchanges with small- and large-dwell volumes has been proposed (“adapted APD”), which improved sodium and fluid removal and lowered blood pressure in adult and pediatric pilot trials (Fischbach et al. 2016).

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## Pharmacological Management

Almost two thirds of pediatric dialysis patients receive chronic antihypertensive medication. There is solid randomized trial evidence that

pharmacological blood pressure lowering provides cardiovascular protection and reduces mortality in adult dialysis patients (Agarwal and Sinha 2009; Heerspink et al. 2009). While beneficial effects are generally seen with all drug classes, some class-specific differences in effectiveness and safety have been noted.

According to the most recent figures of the DOPPS surveillance population,  $\beta$ -blockers are administered in 68%, calcium channel blockers in 51%, and renin-angiotensin-aldosterone system (RAAS) antagonists in 38% of adult HD patients in the USA (Arbor Research Collaborative for Health 2017). The preference for non-RAAS anti-hypertensive drugs is noteworthy since the 2005 NKF-KDOQI guidelines recommended first-line treatment with RAAS antagonists for dialysis patients (National Kidney Foundation 2005). The KDOQI recommendation was based on limited evidence that RAAS blockade may induce greater regression of left ventricular hypertrophy independently of their blood pressure lowering effects (Cannella et al. 1997; Shibasaki et al. 2002) and efficiently reduces sympathetic nerve activity (Klein et al. 2003). More recent studies have questioned the existence of cardioprotective effects of RAAS antagonists by mechanisms beyond blood pressure control (Peters et al. 2014; Zoccali and Mallamaci 2014). On the other hand, a recent outcome analysis of 30,000 US hemodialysis patients documented 10% lower all-cause mortality and 16% lower cardiovascular mortality in patients receiving RAAS antagonists as compared to those treated with  $\beta$  blockers. The findings were confirmed in a second cohort of more than 11,000 patients (Shafi et al. 2017).

One possible explanation of the less popular use of RAAS blockers in the dialysis population may be a perceived less potent hypotensive efficacy of this drug class, especially if administered in salt and fluid overloaded patients. In a placebo-controlled trial, irbesartan did not reduce BP and left ventricular mass more effectively than placebo (Peters et al. 2014). In a head-to-head comparative trial in hemodialysis patients, the beta blocker atenolol tended to show more potent blood pressure lowering action and

cardiovascular risk reduction than the ACE inhibitor lisinopril (Agarwal et al. 2014).

Another concern regarding the use of RAAS blockers in hypertensive dialysis patients is the potential aggravation of the risk of hyperkalemia, one of the most critical complications of ESRD (Sanghavi et al. 2013). The risk of hyperkalemia associated with RAS blockade is retained even in anuric patients. This is likely explained by the inhibition of intestinal potassium elimination, which is increased in renal failure by upregulation of colonic angiotensin receptors (Hatch et al. 1998; Martin et al. 1986). The excess hyperkalemia risk attributable to RAS antagonist use in hemodialysis patients has been quantitated as 2.4-fold in an observational study (Knoll et al. 2002) and 3.2-fold in the HDPAL trial (Agarwal et al. 2014).

Furthermore, the use of RAAS antagonists in dialysis patients may be associated with an increased risk of losing residual renal function due to impaired renal perfusion at times of hypovolemia. This issue is particularly relevant in patients on peritoneal dialysis, who tend to retain residual renal function for extended periods of time. In a recent IPDN registry analysis of 401 children commencing CPD with significant residual urine output, the risk of turning anuric was significantly increased in patients receiving RAS antagonists (Ha et al. 2015) whereas the use of loop diuretics efficiently preserved residual diuresis.

Plasma aldosterone levels are correlated with left ventricular hypertrophy and adverse cardiovascular prognosis (Milliez et al. 2005; Drechsler et al. 2013). In heart failure patients, mineralocorticoid receptor blockers are cardioprotective and efficiently reduce left ventricular mass (Zannad et al. 2011). Two recent randomized trials evaluated the cardioprotective effect of mineralocorticoid receptor blockade in adult dialysis patients. In the DOHAS trial 309 patients were enrolled for low-dose spironolactone or no treatment. During a mean follow-up of 3 years, spironolactone therapy was associated with 62% risk reduction for cardiovascular mortality or hospitalization for cardiovascular causes (HR 0.38, 95% CI 0.17–0.83) (Matsumoto et al. 2014). Notably, the incidence of serious hyperkalemia leading to drug withdrawal

was only 1.9%. Similar results were obtained in a subsequent placebo-controlled trial of add-on low dose spironolactone (25 mg) in 253 hypertensive peritoneal or hemodialysis patients who received multiple antihypertensive medications including RAS blockers. Spironolactone therapy reduced the primary endpoint of cardio- or cerebrovascular death, cardiac arrest, or sudden death by 58% (Lin et al. 2016). Further trials to corroborate the efficacy and safety of mineralocorticoid receptor blockade are currently ongoing.

In patients with hypertension due to volume expansion, dihydropyridine-based calcium channel blockers tend to be most effective in lowering blood pressure due to their vasodilatory action (London et al. 1990). Also, in a study of 2,900 adult HD patients in whom antihypertensive treatment with a calcium channel blocker was started within the first 6 months of hemodialysis, the use of dihydropyridine (vs. nondihydropyridine) agents was associated with a reduced risk of all-cause (adjusted hazard ratio 0.77, 99% CI 0.64–0.93) and cardiovascular mortality (0.86, 0.72–1.02) (Wetmore et al. 2015). On the other hand, it should be emphasized that the use of vasodilatory agents such as calcium channel blockers tends to impair fluid removal capacity on hemodialysis and have been associated with intradialytic hypotension (Bayya et al. 2011). Administration of long-acting agents in the evening has been advocated to minimize interference with intradialytic volume removal.

Antihypertensive agents greatly differ regarding their pharmacokinetic properties and dialyzability. Dialyzable drugs are atenolol and metoprolol, all angiotensin-converting enzyme inhibitors except fosinopril and trandolapril. The beta blocker carvedilol, all calcium channel blocker and all angiotensin receptor blockers are nondialyzable (White 1998; Bakris et al. 2006; Inrig 2010). The use of highly dialyzable  $\beta$ -blockers has been linked with increased arrhythmia risk and mortality in elderly HD patients (Weir et al. 2015). It is usually recommended to withhold antihypertensive drugs with low dialyzability on the morning of HD days, particularly in patients who are prone to intradialytic hypotension. Dialyzable agents

should be administered after hemodialysis sessions. The clinical practice of antihypertensive medication timing is quite heterogeneous. In a survey among US pediatric nephrologists, two thirds of respondents withheld morning medications in HD patients, in particular direct vasodilators and dihydropyridine-calcium channel blockers (Lin et al. 2009). For CPD patients, 80–90% of respondents did not have any preferences concerning the timing of antihypertensive medications.

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## Conclusions

Hypertension and left ventricular hypertrophy are highly prevalent in the pediatric dialysis population. ABPM or home blood pressure monitoring is required to obtain prognostically relevant information about a patient's blood pressure status. Volume status is the primary determinant of blood pressure in dialysis patients; the clinical relevance of additional pathogenic mechanisms such as sympathetic hyperactivity is controversial. The most important measure to maintain normal blood pressure is achievement of the dry weight, which can be facilitated by the use of bioimpedance analysis and intradialytic blood volume monitoring. Dietary salt restriction and avoidance of net salt uptake during dialysis is key to maintain fluid balance. Extended hemodialysis schedules efficiently normalize blood pressure and reverse left ventricular hypertrophy in patients who cannot maintain fluid balance under standard thrice weekly hemodialysis. Pharmacotherapy of hypertension should be reserved to patients with persistent hypertension despite adequate volume status. The preferable first-line antihypertensive drug class is currently unclear; head-to-head comparative trials are urgently needed.

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## Cross-References

- ▶ [Ambulatory Blood Pressure Monitoring Methodology and Norms in Children](#)
- ▶ [Hypertension in Chronic Kidney Disease](#)



- ▶ [Methodology and Applicability of Home Blood Pressure Monitoring in Children and Adolescents](#)
- ▶ [Secondary Forms of Hypertension in Children: Overview](#)
- ▶ [Sequelae of Hypertension in Children and Adolescents](#)

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## Abstract

Hypertension in children after renal transplantation is an important risk factor not only for graft loss but also for cardiovascular morbidity and mortality. The prevalence of posttransplant HTN ranges between 60% and 90%. The etiology of posttransplant HTN is multifactorial – chronic native kidney disease, immunosuppressive therapy, and chronic allograft dysfunction are the most common causes. Casual blood pressure (BP) should be measured at each outpatient visit; however, ambulatory blood pressure monitoring (ABPM) is the best method for BP evaluation in children after renal transplantation, as it often discloses especially nighttime HTN; given this, it should be regularly performed in each transplanted child. All classes of antihypertensive drugs are used in the treatment of posttransplant HTN because it has never been proven that one class would be better than another. The most commonly used antihypertensives are calcium channel blockers. The target BP for transplant children is still a matter of debate; it is recommended to target the same BP as for healthy children, i.e., <90th percentile.

Control of HTN in transplanted children still remains poor – only 20–50% of treated children have normal BP. There is a great potential for improvement of antihypertensive treatment that could potentially result in improvement of both graft and patient survival in children after renal transplantation.

## Keywords

Hypertension • Blood pressure • End-stage renal disease • Children • Kidney transplantation • Cardiovascular morbidity and mortality • Left ventricular hypertrophy

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## Introduction

Hypertension is a common and serious complication in patients after renal transplantation (Baluarte et al. 1994; Kramer et al. 2011; Sorof et al. 1999). It is an important risk factor for cardiovascular morbidity and mortality in transplanted patients (Tutone et al. 2005). Furthermore, it is a strong risk factor for impaired graft survival in adult and pediatric patients (Opelz et al. 1998; Mitsnefes et al. 2001). Cardiovascular events are the second most common cause of death in these patients. Therefore, the treatment of HTN is one of the most important strategies in transplanted children to improve their survival as well as survival of the transplanted grafts.

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## Measurement of Blood Pressure in Transplanted Children

Casual BP should be measured during every outpatient transplant follow-up visit. However, casual BP has its limitations, mainly that it can neither distinguish between true and white coat HTN nor measure BP during sleep or reveal masked HTN. It has been shown in several studies that ambulatory blood pressure monitoring (ABPM) is a better method for BP evaluation than CBP measurement in children after renal transplantation (Mitsnefes et al. 2003; Flynn 2012). The main reasons are the ability of ABPM to reveal white coat or masked HTN and to measure BP during nighttime (detection of isolated nocturnal hypertension). Furthermore, ABPM is superior to casual BP in regard to better correlation with target organ damage such as left ventricular hypertrophy (Mitsnefes and Portman 2003) in children after transplantation. Finally, the results of ABPM are more closely related to renal function in transplanted patients than the results of casual BP (Jacobi et al. 2000). Therefore, regular use of ABPM is recommended in all patients after renal transplantation regardless of the values of casual BP (Lurbe et al. 2009; Flynn 2012; Seeman 2012). ABPM should be performed at least once a year in every transplanted child and about 6 months after every change in antihypertensive therapy.

The predominant type of HTN in transplant children is nocturnal HTN, occurring in 50–70%

of patients (Morgan et al. 2001; Seeman et al. 2006) (Table 1). This finding further stresses the importance of ABPM with its monitoring of BP values during the night. A reduced physiological decrease of BP during the night (blunted nocturnal dip, non-dipping) has been revealed in 30–72% of transplanted children (Morgan et al. 2001; Seeman et al. 2006). Adult transplant patients who are non-dippers have greater left ventricular mass than dippers (Lipkin et al. 1993). However, in a pediatric study, no significant difference in the left ventricular mass index between children with normal and attenuated nocturnal BP dip was found (Seeman et al. 2006). The reproducibility of dipping status in transplanted children is low (Kramer and Berg 2005); therefore, repeated ABPM studies might be needed to describe a transplanted child as a non-dipper. It may be more appropriate to rely on mean BP or BP load while asleep rather than dipping status to guide the treatment of HTN in transplanted children (Flynn et al. 2014).

Home BP measurement is also an important method for measurement of BP. It is increasingly used as a valuable supplement to casual BP and also ABPM in children with chronic renal failure or on renal replacement therapy (Bald et al. 2001; Hooper and Mitsnefes 2015; Wuhl et al. 2004). Bald et al. investigated home BP also in 21 transplanted children and found that it is an important method for control of blood pressure and a valuable supplement to ABPM also for transplanted children. It is especially recommended in children receiving antihypertensive medication to improve control of HTN and to support compliance with the medication; however, there are several problems with home BP such as lack of normative values in children and device validation.

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## Definition and Prevalence of Hypertension in Transplanted Children

The same definition is used for transplanted children as for otherwise healthy children. The prevalence of HTN in children after renal transplantation ranges considerably between 58% and 89% (Baluarte et al. 1994; Kramer et al. 2011; Morgan

**Table 1** Prevalence of different forms of hypertension in children after renal transplantation using ambulatory blood pressure monitoring (ABPM)

Author	Definition of HT	Overall prevalence of HT (n)	Prevalence of nighttime HT (isolated nighttime HT) ((isolated daytime HT))	Prevalence of masked HT	Non-dipping (definition)	Prevalence of untreated HT (among treated pts)	Prevalence of uncontrolled HT	Other findings
Morgan et al. 2001	daytime BP >95th centile for clinic BP or nighttime BP >95th centile for clinic BP minus 10% regardless of drugs	64% (n = 29/45)	64% (22%) ((0%))	n.d.	58% (<10% systolic or diastolic dip) 9%/14%	48%	82%	No significant relationship between ABPM data and LVM
Seeman et al. 2006	daytime or nighttime BP ≥95th centile or use of drugs	89% (n = 32/36)	60% (40%) ((0%))	n.d.	64% (<10% systolic or diastolic dip) 7%/13%	3%	45%	Better control of HT with ACEI and lower CyA/Tac dose/level
McGlothan et al. 2006	24-hr, daytime and nighttime mean BP >95th percentile or systolic load >35% and diastolic load >25% regardless of drugs	21/7% for daytime syst./diast. HT (n=6/2 of 29) 48/41% for nighttime syst./diast. HT	51% (41%) ((n.d.))	n.d.	60% for systolic 37% for diastolic (<10% syst. or diast. dip) 40% for systolic 30% for diastolic (<5.5%) 8%/9%	n.d.	n.d.	Isolated nocturnal HT is more common than daytime HT, children on ACEI/ARB had lower systolic BP than on CCB
Seeman et al. 2007	daytime or nighttime BP ≥95th centile or use of drugs	97% at 2 years (n = 30/31)	n.d.	n.d.	45% at 2 years (<10% systolic or diastolic dip) 10%/14%	0% at 2 years	26%	Improved control of HT can be achieved and is associated with stabilization of graft function

(continued)

**Table 1** (continued)

Author	Definition of HT	Overall prevalence of HT (n)	Prevalence of nighttime HT (isolated nighttime HT) ((isolated daytime HT))	Prevalence of masked HT	Non-dipping (definition) systolic/diastolic dip	Prevalence of untreated HT (among treated pts)	Prevalence of uncontrolled HT	Other findings
Balzano et al. <a href="#">2011</a>	Daytime or nighttime BP $\geq$ 95th centile or drugs	82% (n = 4/22) at 9 years follow-up	n.d.	n.d.	n.d.	5%	18% at 9 years follow-up	Very low prevalence of LVH (4%) and lack of progression of cIMT might reflect positive effect good BP control
Hamdani et al. <a href="#">2016</a>	a) daytime or nighttime BP $\geq$ 95th centile and daytime or nighttime BP load $\geq$ 25% b) 24hr BP load $\geq$ 25%	a) 36% (n=80/221) b) 46% (n=102/221)	a) n.d. b) n.d.	a) 25% b) 32%	52% for systolic BP 28% for diastolic BP (<10% systolic or diastolic dip) 10%/15%	12%	49%	Very high prevalence of LVH (75%) among untreated sustained hypertensive pts. and prevalence of LVH in controlled HT (37%) similar to that in uncontrolled HT (44%)
<b>Median values from all studies</b>	n.a.	64%	60% (33%) ((0%))	29%	60% (for all definitions) 7%/13%	12%	45%	n.a.

HT hypertension, BP blood pressure, ABPM ambulatory blood pressure monitoring, n.d. not determined, n.a. not applicable, LVM left ventricular mass, CyA cyclosporine A, Tac tacrolimus, Tx transplantation, ACEI angiotensin converting enzyme inhibitors, ARB angiotensin receptor blockers, CCB calcium channel blockers, cIMT carotid intima media thickness



et al. 2001; Seeman et al. 2006; Sinha et al. 2012; Sorof et al. 1999). The reason for the wide range in the prevalence of HTN is based mainly on the different methods of BP measurement and different definitions of HTN used in various trials. Studies using casual BP measurements alone always report lower prevalence of HTN than studies that used ABPM. This phenomenon clearly underlines the importance of ABPM since it also measures BP during the night when BP is often increased in transplanted patients (McGlothan et al. 2006).

Patients' BP status should be further classified based upon current antihypertensive drug treatment and measured BP level. Children on antihypertensive drugs with normal current BP should be regarded as having *controlled* HTN, and children on antihypertensive drugs with elevated current BP should be regarded as having *uncontrolled* HTN. The main reason for this differentiation is the fact that it has been shown in several trials that transplanted patients with controlled HTN have similar graft survival as spontaneously normotensive patients (i.e., normal BP without antihypertensive drugs). In contrast, patients with uncontrolled HTN have significantly worse graft survival (Mitsnefes et al. 2003; Vianello et al. 1993). Therefore, using only one category of HTN (regardless of the therapeutic control of HTN) or antihypertensive drugs as the only criterion for definition of HTN without knowing the current level of BP would lead to misinterpretation of the importance of the influence of BP on the overall prognosis of transplanted patients. The prevalence of hypertension can change also over the time after transplantation; it usually decreases but can also increase during long-term follow-up (Kaidar et al. 2014; Kramer et al. 2011; Sinha et al. 2012).

## Etiology and Pathogenesis of Hypertension in Transplanted Children

The etiology of posttransplant HTN is multifactorial (Baluarte et al. 1994; Gordjani et al. 1990; Seeman 2009; Sorof et al. 1999). The main causes are summarized in Table 2.

Hypertension prior to transplantation caused mainly by the diseased native kidney is believed to be a significant risk factor for the presence of HTN after successful renal transplantation (Gordjani et al. 1990; Seeman 2012). Children receiving kidneys from deceased donors are more frequently hypertensive than children receiving grafts from living donors (Bald et al. 2001; Gordjani et al. 1990; Sorof et al. 1999). The lower prevalence of HTN among children after living donor transplantation could be one of the reasons for better graft survival of the living donor grafts. This hypothesis is supported by the results of a single-center study which shows that posttransplant HTN is, together with episodes of acute rejection, the only independent determinant of graft survival in children after living donor transplantation (El-Husseini et al. 2005).

Corticosteroids are a well-known risk factor for posttransplant HTN, with the major mechanisms likely being related to sodium retention or increase in cardiac output and renal vascular resistance. Elimination of steroids in stable patients showed reduction of BP in adult as well as in pediatric patients (Hocker et al. 2004; Kasiske and Ballantyne 2002), and children transplanted under a steroid avoidance immunosuppressive protocol showed improvement in HTN (Sarwal et al. 2012). In a cross-sectional study, the patients on alternate dose steroid treatment showed significantly lower prevalence of HTN than children on

**Table 2** Causes of hypertension in transplanted children

Recipient's native kidney
Immunosuppressive drugs (steroids, cyclosporine A, tacrolimus)
Graft dysfunction (acute rejection, chronic allograft dysfunction)
Kidney from cadaveric, borderline, or hypertensive donor
Renal graft artery stenosis
Overweight/excessive post-transplant weight gain
Genetic factors (primary hypertension, genes of RAAS)
Recurrent or de novo renal disease (e.g. IgA nephropathy, focal segmental glomerulosclerosis)
Others (e.g. polycythemia, pyelonephritis, ureteric obstruction, lymphocele)

RAAS renin-angiotensin-aldosterone system

daily steroid medication (Morgan et al. 2001), and another study showed that conversion from daily to alternate dose steroid therapy significantly reduces BP (Curtis et al. 1976). Therefore adoption of steroid sparing or steroid-free immunosuppression regimens can be considered a treatment strategy for improving control of BP in transplanted children.

With the introduction of the calcineurin inhibitor cyclosporine, there has been a dramatic increase in the prevalence of posttransplant HTN (Gordjani et al. 1990). Gordjani et al. showed in their large single-center study on 102 children that high trough levels of cyclosporine ( $>400$  ng/ml) were associated with a significantly higher incidence of HTN in comparison to children with levels  $<400$  ng/ml (91% vs. 57%). The newer calcineurin inhibitor tacrolimus also has hypertensinogenic effects similar to cyclosporine. In the only randomized controlled trial comparing cyclosporine- and tacrolimus-based immunosuppression in pediatric renal transplanted patients, there were no significant differences in the prevalence of HTN between children treated with cyclosporine and those with tacrolimus (Trompeter et al. 2002). Newer immunosuppressive agents such as mycophenolate mofetil, sirolimus, or everolimus do not have effects on BP, and therefore their use is a further option to improve control of HTN in transplanted children (Buscher et al. 2004).

Renal graft dysfunction is another risk factor for posttransplant HTN; however, there is a dual relationship between BP and graft dysfunction. On the one hand, graft dysfunction elevates BP, while on the other hand, elevated BP accelerates the decline of graft function. In adults, impaired graft function is associated with elevated BP and increased risk of HTN (Cheigh et al. 1989; Jacobi et al. 2000; Vianello et al. 1993). In a single-center study, Mitsnefes et al. did not find any difference in mean calculated glomerular filtration rate or acute rejection episodes between normotensive and hypertensive children (Mitsnefes et al. 2003). However, hypertensive children had reduced allograft function (glomerular filtration rate  $\text{GFR} < 50$  ml/min/1.73 m<sup>2</sup>) more frequently than normotensive patients, whereas children with

normal BP more frequently had normal graft function ( $\text{GFR} > 75$  ml/min/1.73 m<sup>2</sup>).

Current body weight or change of body weight is a well-known and potent determinant of BP level in adults and children (Lurbe et al. 1998), and most children gain weight after renal transplantation (Hanevold et al. 2005). Therefore, control of body weight should be recommended in all children after renal transplantation to improve BP control (Wilson et al. 2010).

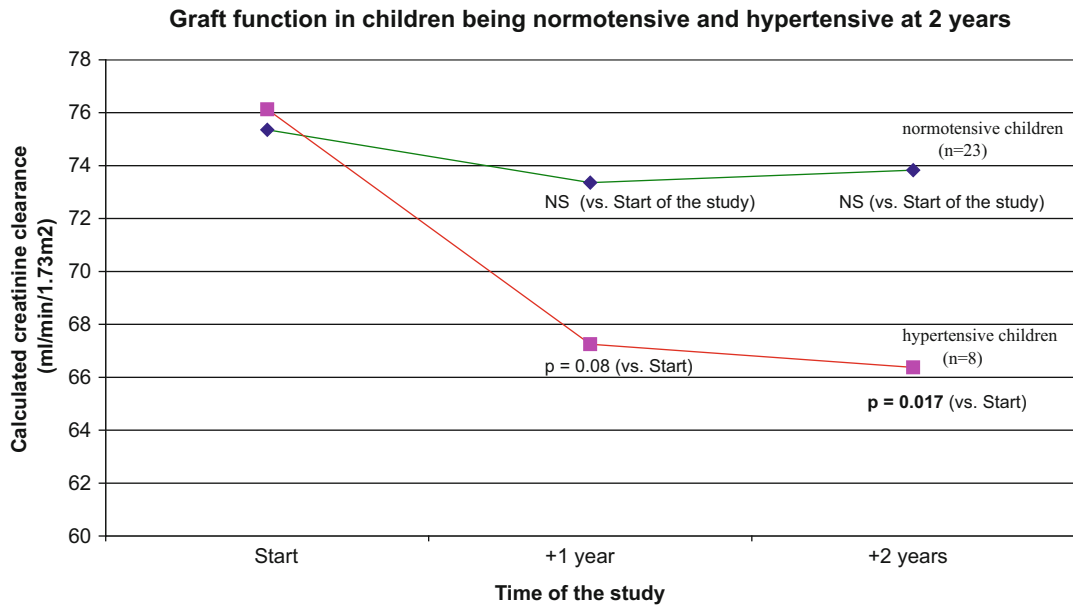
Stenosis of the graft artery has become a rare cause of HTN with current surgical technique using aortic patches (Fung et al. 1995). Doppler ultrasonography, magnetic resonance, and CT angiography are noninvasive techniques that can easily diagnose this cause of HTN. The treatment of choice is percutaneous transluminal angioplasty; surgery should be reserved for cases of angioplasty failure.

The development of recurrent or de novo glomerulonephritis (mainly IgA nephropathy or focal segmental glomerulosclerosis) may be associated with the occurrence of HTN, although these conditions are not common causes of significant posttransplant HTN (Ponticelli and Glassock 2010).

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## Complications of Hypertension in Transplanted Children

Hypertension is a strong predictor of graft loss. The most robust evidence comes from the results of the large multicenter Collaborative Transplant Study (CTS) published by Opelz et al. (1998) which showed that there is a linear negative relationship between casual BP and renal graft survival. This is true not only for adults but also for children  $<18$  years. This relationship between BP and graft survival has been later confirmed by many other studies in adult and pediatric patients (Tutone et al. 2005; Mitsnefes et al. 2003). Hypertensive pediatric transplant recipients have the worse long-term graft survival than normotensive recipients (Fig. 1). The results from the NAPRTCS registry showed that the use of antihypertensive medication (the definition used for HTN in this retrospective analysis) was associated with higher rates of graft failure (Sorof et al. 1999). Increased BP is therefore clearly



**Fig. 1** Graft function in children being normotensive and hypertensive at 2 years

associated with decreased graft survival. Despite these clear findings, it is still a matter of debate whether posttransplant HTN is a real cause of chronic allograft dysfunction or only the result of renal dysfunction or both. Several findings from retrospective studies such as from the study done by Mitsnefes et al. (2003) showing that HTN is associated with allograft failure in children with normal graft function but not in children with severely impaired graft function suggests that HTN is not only a marker of graft dysfunction but also a direct cause of renal graft damage (Fig. 1).

Similar to the general population, HTN is also associated with increased cardiovascular morbidity in transplanted patients (Wilson and Mitsnefes 2009). Left ventricular hypertrophy (LVH) is a frequent type of cardiac end-organ damage in hypertensive children after renal transplantation, occurring in 50–82% children (Morgan et al. 2001; Seeman et al. 2006). Matteucci et al. (1999) found a correlation between left ventricular mass index (LVMI) and mean 24-h systolic BP, but Morgan et al. (2001) could not demonstrate any relationship between LVMI and ambulatory BP data. However, in another study of Kitzmueller et al., there was a correlation between LVMI and

ABPM data at repeated measurement but not at baseline, suggesting that control of BP, i.e., change of BP level during longitudinal follow-up, is important for the maintenance of the myocardial architecture (Kitzmueller et al. 2004). Hypertensive transplanted children also have a greater prevalence of newer markers of cardiovascular damage such as increased cIMT, coronary calcifications, or increased pulse wave velocity (Kis et al. 2008; Mitsnefes et al. 2004; Litwin et al. 2005; Dvorakova et al. 2012).

Hypertension is also a risk factor for increased cardiovascular mortality seen in transplanted adult patients (Kasiske et al. 1996). Similar studies in children are rare. The Dutch Cohort Study has demonstrated that HTN is one of the most powerful risk factor for cardiovascular morbidity and mortality in children after renal transplantation (Groothoff et al. 2002). In this study cardiovascular events were the most common cause of death, and hypertensive children had a three times higher risk of overall mortality than normotensive children. Additional studies are needed for more information on the causal role of HTN in the high cardiovascular morbidity and mortality in transplanted children.

## Evaluation of Hypertensive Children After Renal Transplantation

Casual BP should be measured during every outpatient visit, and regular use of ABPM is recommended in all patients after renal transplantation regardless of the values of casual BP because of high prevalence of nocturnal or masked HTN. This recommendation has been firstly used by the European Society of Hypertension (ESH) in its pediatric recommendations (Lurbe et al. 2009) and has been recommended also by other experts (Flynn 2012; Seeman 2012) and also by the most recent ESH Guidelines (Lurbe et al. 2016). ABPM should be performed at least once a year and about 6 months after change of antihypertensive medication to reassess control of HTN after modification of antihypertensive therapy.

The diagnostic evaluation of HTN in transplanted children should consider the multiple etiologies of posttransplant HTN (Table 2). Renal graft artery stenosis (Doppler renal ultrasonography, magnetic resonance, or CT angiography), high levels of immunosuppressive drugs (steroids, cyclosporine A, tacrolimus), chronic graft dysfunction (serum creatinine, event, graft biopsy), or ureteric obstruction (renal ultrasonography, renal scan) should be excluded in the differential diagnostics of HTN in a transplanted child. Echocardiography should be assessed at least once a year to determine the presence or absence of hypertensive target organ damage on the heart (Wilson and Mitsnefes 2009). Fundoscopy should be done in children with hypertensive crisis or posterior reversible encephalopathy syndrome (PRES). Moreover, acute graft dysfunction (serum creatinine, graft biopsy) or recurrent or de novo renal disease such as IgA nephropathy and focal segmental glomerulosclerosis (urinalysis, graft biopsy) should be excluded in the transplant patient who develops de novo HTN after being normotensive initially.

Newer methods for the detection of cardiovascular disease such as assessment of cIMT or PWV should also be considered research techniques in pediatric transplant patients.

## Treatment of Hypertensive Children After Renal Transplantation

There is clear evidence from the observational studies on the correlations between BP and cardiovascular morbidity and mortality and graft function that posttransplant HTN must be treated. If an identified treatable cause of HTN is detected (such as renal graft artery stenosis, recurrence of primary disease, ureteric stenosis), the primary disease leading to BP elevation should be treated.

Many other issues on the treatment of HTN in children after renal HTN are less clear or even controversial. For example, there are no studies comparing different classes of antihypertensive drugs in children after renal transplantation; therefore, it is not known whether one class of drugs is better than another in transplanted patients.

Historically, calcium channel blockers (CCB) have been considered the drugs of choice for posttransplant HTN because they counteract the afferent arteriolar vasoconstriction caused by calcineurin inhibitors and reduce their nephrotoxicity (Curtis 1997; Silverstein et al. 1999).

There has been some concern that angiotensin converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs) may lead to deterioration of graft function in patients with undiagnosed graft artery stenosis or due to the preferential efferent arteriolar vasodilation and reduction of intraglomerular pressure. However, it has been demonstrated that ACE inhibitors are safe and effective drugs in adult as well as pediatric transplant patients (Stigant et al. 2000; Arbeiter et al. 2004). Moreover, they can reduce proteinuria which in addition to HTN is another treatable risk factor for impaired graft survival (Seeman et al. 2010). Furthermore, ACE inhibitors and ARBs can slow progression of chronic native kidney diseases mainly by long-term reduction of intraglomerular pressure and renal fibrosis (Simões et al. 2016; Sun et al. 2016). The ability of ACE inhibitors to slow progression of chronic allograft dysfunction, which is the most common cause of late graft loss, has never been proven in a prospective interventional trial in adult or pediatric patients. Some retrospective

studies have shown promising results, such as stabilization or even an improvement in patient survival and graft function in patients with chronic allograft dysfunction (Arbeiter et al. 2004; Heinze et al. 2006; Suszynski et al. 2013). However, the results from the CTS published recently did not show any improvement of patient or graft survival in patients treated with ACE inhibitors (Opelz et al. 2006). Therefore, this issue is still controversial and needs prospective interventional trials to resolve this controversy.

ARBs are less frequently used in adults and children after renal transplantation than ACE inhibitors (Calvino et al. 2000; Seeman et al. 2009); however, they seem to have similar risks and benefits as ACE inhibitors. Beta-blockers are also effective drugs in transplanted patients (Hausberg et al. 1999). However, beta-blockers are not able to reduce proteinuria as ACE inhibitors do. A further disadvantage of beta-blockers is their negative metabolic effects (increased lipid levels or impaired glucose tolerance), which may further contribute to the increased risk of cardiovascular disease in these patients.

Sodium retention is often present after renal transplantation, and therefore diuretics are important antihypertensive drugs in these patients as well. Thiazide diuretics should be preferred in patients with normal graft function, whereas loop diuretics should be given in patients with impaired graft function. Diuretics may also have detrimental metabolic effects such as hyperlipidaemia, hyperuricaemia, or hyperglycaemia. Potassium-sparing diuretics are used rarely due to their risk of hyperkalemia.

All five major classes of antihypertensive drugs can therefore be used in transplanted patients. Posttransplant HTN has a multifactorial etiology and is often severe; therefore, combination therapy is usually needed to control it. Which drug should be used as a first-line treatment remains the individual decision of the physician because it has not been consistently shown that one class is better than the other in renal transplant recipients (Curtis et al. 1976; Seeman 2009). In most pediatric renal transplantation centers, the most commonly used antihypertensive drugs are

CCB, which are given to 38–65% of transplanted children (McGlothan et al. 2006; Morgan et al. 2001; Seeman et al. 2006). The second most commonly prescribed drugs are ACE inhibitors and beta-blockers. Diuretics and ARB are given less frequently to transplanted children.

Non-pharmacological lifestyle measures (reduction of increased body weight, reduction of salt intake, regular physical activity) should be encouraged even during antihypertensive drug therapy as they target the risk factors not only for HTN but also for cardiovascular morbidity and mortality of the patients (obesity, increased salt intake, physical inactivity) (Neale et al. 2016).

Minimizing hypertension-inducing immunosuppressive drugs, such as corticoids or calcineurin inhibitors, is another additional option on how to improve the efficacy of hypertension therapy (Hocker et al. 2004, 2010; Sarwal et al. 2012; Hooper and Mitsnefes 2015). However, great attention needs to be paid when manipulation with the immunosuppressive drugs happen due to the risk of acute rejection.

It is still a matter of debate what should be the target BP for patients after renal transplantation. The National Kidney Foundation Task Force on Cardiovascular Disease recommends a target BP level <130/85 for adult renal allograft recipients and <125/75 for proteinuric patients similar to guidelines for the management of HTN in patients with diabetic nephropathy (Task force report 1998). However, there are no prospective interventional trials showing that target BP lower than the conventional cutoff of 140/90 improves graft function or long-term graft survival. The same is true also for pediatric renal transplant recipients. The ESCAPE trial showed that reduction of ambulatory 24-h BP <50th percentile leads to significantly slower progression of CKD in children compared to BP between the 50th and 95th percentiles (Wuhl et al. 2009). However, it is not known whether these results can be extrapolated to transplanted children as no similar study has been published yet in kidney graft recipients. An ongoing study is investigating this issue (ESCORT trial – effects of strict control of blood pressure in pediatric renal transplant recipients).

The current recommendation of the European Society of Hypertension recommends target BP <75th percentile for children with CKDs without proteinuria and <50th percentile for children with proteinuria (Lurbe et al. 2016). While no such consensus recommendation has yet been made for the management of HTN after renal transplantation, we would recommend that the target BP for healthy children (<90th percentile) should be achieved in transplanted children (Flynn 2006; Seeman et al. 2007), pending publication of results of the ESCORT trial (see below).

The control of HTN in children after transplantation is still not adequate. Only a minority of children treated for HTN after kidney transplantation has BP at least below the target BP <95th percentile (Seeman 2012; Seeman et al. 2006; Sinha et al. 2012). The prevalence of persistent HTN despite antihypertensive treatment (i.e., prevalence of uncontrolled HTN) ranged between 27% and 37% in the recent pediatric studies using casual BP and as high as 45–82% in pediatric studies using ABPM (Morgan et al. 2001; Seeman 2012; Seeman et al. 2006) (Table 1). This means that only 18–55% of children after renal transplantation had ambulatory HTN controlled by drugs with BP at least <95th percentile. These data suggest that there is a high potential for improvement of antihypertensive therapy in children after renal transplantation.

The reasons for the insufficient antihypertensive therapy in transplanted patients have not been thoroughly investigated. Many factors, such as chronic allograft dysfunction, need for lifelong use of immunosuppressive drugs that increase BP (steroids, cyclosporine, tacrolimus), obesity, salt retention, renin secretion from diseased native kidneys, and the fear of ACE inhibitors or ARB in transplanted patients are often discussed as the major reasons for inadequate BP control in transplanted patients. Lastly, noncompliance (non-adherence) can play an important role in the control of HTN, particularly in adolescent patients. Therefore, compliance (adherence) not only to the recommended immunosuppressive medications but also to antihypertensive drugs should be reviewed during every outpatient visit. A system-based approach to managing

hypertension in children following kidney transplantation has been described by Hooper and Mitsnefes that may improve the usually poorly controlled blood pressure in transplanted patients (Hooper and Mitsnefes 2015). This approach includes five essential elements: appropriate measurement of BP including ABPM, identification and classification of uncontrolled hypertension including nocturnal hypertension, antihypertensive therapy including assessment of response of therapy, appropriate minimization of medications that cause hypertension, and self-management report.

An important issue is whether the poor control of HTN can be improved and whether improved control of HTN can stabilize or even improve graft function or cardiac complications. Results from the CTS group showed that improved control of BP is associated with improved long-term graft and patient survival in adults (Opelz et al. 2005). However, a large retrospective observational study from the Midwest Pediatric Nephrology Consortium has demonstrated that transplanted children who required antihypertensives had worse graft dysfunction than those who did not require antihypertensive medication (i.e., had spontaneous normotension), even in those whose BP was within normal levels (i.e., had controlled hypertension) (Hamdani et al. 2016). This may reflect an effect of previously untreated or inadequately treated hypertension on worsening graft function and indicate the need for even more aggressive treatment of posttransplant hypertension.

Four recent prospective interventional studies have demonstrated promising result on this issue in children. In the first prospective interventional trial on intensified treatment of HTN, it was shown that the ambulatory BP could be significantly reduced after 2 years by increasing the number of antihypertensive drugs, especially ACE inhibitors and diuretics, and that children who remained hypertensive during a 2-year interventional trial on BP control lost significant graft function compared to children in whom BP was lowered to normotensive range despite similar graft function at the beginning of the trial (Fig. 1) (Seeman et al. 2007). Therefore, adequate

BP control is as essential as immunologic surveillance in the long-term care of transplanted children. In the second study, left ventricular mass index improved and the prevalence of LVH decreased from 54% to 8% in transplanted children in comparison to the same children being on dialysis, and these positive changes in cardiac structure were associated with decrease of systolic and diastolic BP index (Becker-Cohen et al. 2008). An even more impressive result was seen in an observational long-term study, where the regular annual use of ABPM over 9 years resulted in an improvement of the control of HTN to 82%, with a decrease of prevalence of LVH to 4% (Balzano et al. 2011). These recent encouraging data show that in transplanted children, the control of HTN and development of cardiac target organ damage can be improved in clinical practice. Furthermore, the results of the fourth, still ongoing ESCORT trial (3-year prospective randomized controlled study on the effects of strict BP control in pediatric renal transplant recipients) will show whether strict BP control (i.e., target 24 h BP <50th percentile similar to that used in the ESCAPE trial) can slow down the progression of chronic allograft dysfunction. The preliminary 2-year results have demonstrated that in the majority of transplanted children, the 24 h BP can be lower below the 50th percentile without any adverse effect (Seeman et al. 2015).

## Conclusion

Hypertension is a common complication in children after renal transplantation; it affects 60–90% of transplanted patients. Blood pressure should be measured in a transplanted child as casual BP at each outpatient visit but also regularly by ABPM regardless of the values of casual BP due to the high prevalence of nocturnal and masked HTN. Hypertension is an important risk factor for cardiovascular morbidity, mortality, and graft survival. Treatment of hypertension should start always with pharmacologic agents; the target BP for transplanted children is still unknown; however, it should be at least similar to healthy children.

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## Abstract

High blood pressure in children is caused by vascular abnormalities in the aorta such as coarctation or mid-aortic syndrome or in the renal arteries in a significant proportion of cases. The underlying causes are mostly unknown but thought to be an abnormality in the blood vessel wall often called fibromuscular dysplasia. Inflammation in the vessel wall, vasculitis, can also cause hypertension. Vascular abnormalities are important to diagnose as in most cases they are amenable to surgery or angioplasty.

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## Keywords

Renovascular hypertension • Renal artery stenosis • Mid-aortic syndrome • Angiography • Renal vein renins • Angioplasty • Stenting • Coarctation aorta

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## Introduction

The causes of vascular hypertension include narrowing of the renal arteries, narrowing of the abdominal part of the aorta (mid-aortic syndrome), narrowing of the aortic arch (coarctation of the aorta), and aneurysmal disease (Gill et al. 1976; Wyszynska et al. 1992). We will discuss these different entities here.

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## Renovascular Disease

Renovascular disease (RVD) is a relatively uncommon but important cause of hypertension in children as it is often treatable with angioplasty or surgery; for a more extensive review, please see (Tullus et al. 2008). The extent of RVD ranges from narrowing of only one renal artery, found in a relatively small group of children, to the larger group of children with extensive involvement of several parts of their vascular tree (Vo et al. 2006). Both renal arteries are affected in between 53% and 78% of cases, and intrarenal small artery disease is found in a third of children

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(Daniels et al. 1987; Deal et al. 1992). A significant proportion (20–48%) have associated mid-aortic syndrome (MAS) (Panayiotopoulos et al. 1996; Sethna et al. 2008), which includes narrowing of the abdominal aorta. Stenosis of the celiac axis and the superior and inferior mesenteric arteries occurs in 53% of cases with RVD, and cerebral artery disease is found in at least 20%. Eleven (78%) of 14 children with occlusive cerebrovascular disease had concurrent renal artery disease in one report (Willsher et al. 2013). The mechanisms for the hypertension in renovascular disease are increased secretion of renin due to hypoperfusion, with consequent retention of sodium, leading to volume expansion and vasoconstriction induced by angiotensin II. Increased sympathetic nerve activity can also play a role.

## Etiology

There are many causes of RVD in children, and they differ from those in adults, in whom atherosclerotic disease predominates (Table 1) (Tullus

**Table 1** Causes of renovascular hypertension in children (Tullus 2013; Tullus et al. 2008)

Fibromuscular dysplasia
<b>Syndromic</b>
Neurofibromatosis type 1 (NF-1)
Williams syndrome
Tuberous sclerosis
Alagille syndrome
Other syndromes
<b>Vasculitis</b>
Takayasu disease
Polyarteritis nodosa
Other systemic vasculitides
Extrinsic compression
Wilms' tumor
Lymphoma
Other tumors
<b>Other causes</b>
Postradiation
Post-umbilical catheters
Trauma
Transplant renal artery stenosis

2013; Tullus et al. 2008). Certain syndromes, in particular neurofibromatosis type 1 and Williams syndrome, are overrepresented among children with RVD even if most children with these syndromes do not show RVD (Criado et al. 2002; Daniels et al. 1985; Kurien et al. 1997). Acquired conditions like tumors, radiation, and trauma can also cause significant RVD.

The main causes of RVD are fibromuscular dysplasia (FMD) and Takayasu arteritis (TA) (Tullus 2013). The incidence of these conditions varies markedly in different parts of the world (Tullus 2013). In many centers, FMD is most common (Sandmann et al. 2014; Slovut and Olin 2004) while in other parts of the world, e.g., India, TA is the most common diagnosis (Hari et al. 2000; McCulloch et al. 2003). The reason for this regional variation is not clear. It does not seem to be related to genetic differences, as TA is not common in children who have moved from East Asia to Europe. Different infectious disease patterns or different diagnostic traditions are two other possible explanations.

## Fibromuscular Dysplasia

Fibromuscular dysplasia is defined as a non-atherosclerotic noninflammatory vascular disease (Olin and Sealove 2011; Slovut and Olin 2004). It typically affects the renal and the carotid arteries, but it can involve almost every artery in the body (Olin and Sealove 2011; Slovut and Olin 2004). In adult patients it affects mainly women, with 91% female predominance (Olin et al. 2014). An American registry has been established with data on 447 patients published to date. Two hundred ninety four (66%) showed renal artery involvement (Olin et al. 2012). Thirty-three children have been included in the registry (Green et al. 2016). They showed hypertension significantly more often than the adult patients, and boys were also nearly as commonly affected as girls. The vascular disease was also more widespread in the children with the mesenteric arteries involved in 39% and the aorta in 26% of cases.

FMD is regarded as a rare disease, but some data from healthy potential kidney donors suggest that up to 6.6% of adult women could be affected (Blondin et al. 2010; Neymark et al. 2000).

The etiology of FMD is unknown, but it has been thought to be, at least in part, a genetic disorder as outlined below (Olin et al. 2014).

FMD affects one or several layers of the blood vessel wall. It is mostly a diagnosis of exclusion as the typical pattern on angiography with so-called string of beads (Fig. 1a) often is not present. It is also uncommon to have pathological confirmation of the diagnosis as only a minority of children will have surgery. The vascular disease is progressive in many children. The number of blood vessels, renal and extrarenal, that are involved can increase, and the severity of the lesion is often seen to worsen over time. There are no known ways to predict the further course in a single child.

### Takayasu Arteritis

TA is in children the by far most common large vessel vasculitis (Forsey et al. 2011; Gulati and Bagga 2010). Occasional cases of polyarteritis nodosa can also have large vessel involvement. TA is a chronic granulomatous inflammation that involves the aorta and its major branches. It is quite unusual in a Western population, one to two cases/million per year, but regarded as more common in, e.g., eastern Asia and India.

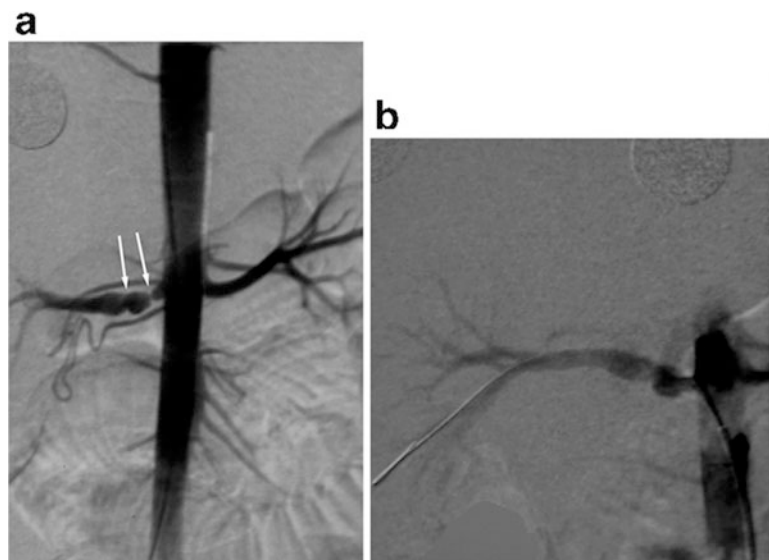
TA is clinically divided into an early systemic phase and a late occlusive (pulseless) phase.

The early phase is characterized by nonspecific symptoms such as low-grade fever, weight loss, arthralgia, and fatigue. Many patients have anemia and increased erythrocyte sedimentation rate (ESR) during this phase. Half of the patients are however not diagnosed before the chronic phase (Forsey et al. 2011; Gulati and Bagga 2010). No signs of inflammation can be detected in the chronic phase, either by clinical symptoms or by laboratory testing.

The vascular bed most commonly involved in TA is the subclavian arteries, but it often includes narrowing of the aorta, common carotids, renal arteries, celiac axis, and pulmonary arteries (Kerr et al. 1994). The presenting symptoms of TA in the silent phase are similar to those of FMD with hypertension and sometimes secondary heart failure or neurological events.

Several different criteria have been developed for the diagnosis of TA. The American College of Rheumatology (ACR) in 1990 published their classification criteria (Arend et al. 1990). They give six criteria out of which three must be fulfilled. One is age below 40 years, and the others are all related to the narrowing of the blood vessels as claudication or an abnormality on the arteriogram. European League against Rheumatism/Paediatric Rheumatology European Society (EULAR/PReS) in 2006 published their

**Fig. 1** (a) Typical beaded appearance of a renal artery with severe stenosis, (b) after treatment with angioplasty



classification criteria (Ozen et al. 2006). They proposed a mandatory criterion of an angiographic abnormality and at least one of four features: decreased pulses/ Claudication, blood pressure difference of >10 mmHg, bruit, and hypertension. After reevaluation one additional criterion was added: acute phase reactant, ESR >20, or CRP above normal value (Ozen et al. 2010) thus quite soft signs of inflammation.

It should be noted that both the ACR and the EULAR/PRES have published *classification* criteria thus implying that the diagnosis of a vasculitis should be made before the classification criteria are applied to define the specific type of vasculitis in the child (Arend et al. 1990; Ozen et al. 2006; 2010). Several recent reviews have however used these criteria as *diagnostic* criteria (Forsey et al. 2011; Gulati and Bagga 2010).

The differential diagnosis between FMD and TA can thus be quite difficult. Imaging of the thickness of the blood vessel wall with intravascular ultrasound, computed tomography angiography (CTA), or magnetic resonance angiography (MRA) can sometimes be helpful in distinguishing these two entities from each other by demonstrating edema of the vessel wall. A [<sup>18</sup>F]fluorodeoxyglucose positron emission tomography (FDG PET) scan can also be helpful to establish the presence of inflammation in the blood vessel wall (Blockmans 2011).

Children with TA in the active phase should be treated with anti-inflammatory drugs such as steroids, azathioprine, mycophenolate mofetil, and cyclophosphamide (Forsey et al. 2011; Gulati and Bagga 2010). TNF $\alpha$  blockers have also been tried (Tanaka et al. 2006). There are no reports of improvement of the vascular lesions with immunosuppressive treatment. It is therefore important to treat the narrowed blood vessels (see below) when the inflammation is under control (Tullus 2013, 2015).

## Genetic Considerations in Renovascular Hypertension

A minority of cases of renovascular hypertension in children are related to monogenic disorders

which confer an increased risk of arterial narrowing and resultant hypertension. Examples of such conditions include neurofibromatosis type 1 (Fossali et al. 2000) and Williams syndrome (Donnai and Karmiloff-Smith 2000).

The majority of renovascular hypertension in children is currently understood to be related to fibromuscular dysplasia. This encompasses a broad phenotype, and its genetic and pathologic basis is not well understood (Olin et al. 2014). Studies in adult patients with fibromuscular dysplasia, and US registry data, indicate that inherited factors probably play a role with a family history of an affected first-degree relative in 7–11% of all cases (Olin et al. 2012; Pannier-Moreau et al. 1997; Perdu et al. 2007). A number of genetic variants have been reported in association with fibromuscular dysplasia in case reports and small series. These include variants in genes encoding the angiotensin-converting enzyme (Bofinger et al. 2001) and  $\alpha$ -1 antitrypsin (Schievink et al. 1994). These associations have however not been replicated in larger studies (Perdu et al. 2006). Other candidate genes have been evaluated including ACTA2, the gene for smooth muscle cell  $\alpha$ -actin, and genes associated with connective tissue disease including COL31A and transforming growth factor (TGF)- $\beta$ 1 and  $\beta$ 2 (Hiratzka et al. 2010; Marks et al. 2011; Poloskey et al. 2012). No replicable associations have been found to date.

In summary, while monogenic disorders account for a small minority of renovascular hypertension in children, the genetic basis and pathophysiology of fibromuscular dysplasia remains unclear. It is anticipated that the application of molecular genetics in future studies will yield novel information on the pathogenesis of fibromuscular dysplasia in due course (Olin et al. 2012).

## Presentation

Children with RVH often present with very high BP; it is not uncommon to have systolic blood pressure well above 200 mmHg with maximum blood pressure even reaching 300 mmHg.

Symptoms at presentation are very variable. Importantly a large group of the children (26–70%) are totally asymptomatic at the time of diagnosis, and the hypertension is discovered as an incidental finding (Shroff et al. 2006; Stadermann et al. 2010). At the other end of the spectrum, some children present with very severe potentially life-threatening cerebral or cardiac symptoms such as stroke and heart failure (Deal et al. 1992; Estepa et al. 2001; McTaggart et al. 2000; Shroff et al. 2006).

We have seen several children with documented blood pressures above 200 mmHg systolic sustained over several years without any treatment or investigations having been initiated. These children have all been asymptomatic, and it seems as if the treating doctor did not believe that the blood pressure could really be true.

Renal artery stenosis can also affect kidney transplant recipients and should be considered in transplanted children who require two or more antihypertensive drugs for blood pressure control (Ghirardo et al. 2014).

## Aneurysmal Disease

Aneurysmal disease is a rare cause of hypertension in children. Arterial aneurysms in children can result from vascular insults such as proximal vascular stenosis, trauma, fungal infection, and vasculitic or connective tissue disease such as Kawasaki disease and Ehlers-Danlos syndrome (Davis et al. 2016). In the US registry of fibromuscular dysplasia which comprises mostly adult patients, 42% had an associated arterial aneurysm or dissection. The most common sites of aneurysm were the extracranial carotid, renal, and intracranial arteries (Kadian-Dodov et al. 2016). Abdominal aortic aneurysms are very rare in children and are associated with significant morbidity and mortality (Ye et al. 2012). Surgical management in a specialist center is necessary.

The risk of rupture of renal arterial aneurysms and the indications for intervention to prevent it are not well defined. One group reports *ex vivo* renal artery repair with autotransplantation for

renal artery branch aneurysms to ameliorate the risk of rupture (Duprey et al. 2016); however, others advocate a conservative approach in the absence of complications such as hypertension. We have treated a number of children at our institution with widespread aneurysmal disease with interventions tailored to the individual case following multi-professional consensus. These interventions have included endovascular coiling, aneurysm excision, and bilateral nephrectomy followed by allotransplantation in severe cases.

## Diagnostic Imaging

Digital subtraction angiography (DSA) is the most reliable way to diagnose RVD, and it is the only method that can define the full extent of the vascular disease (Fig. 1) (Shahdadpuri et al. 2000; Vo et al. 2006). The sensitivity and specificity of other imaging methods is presented in Table 2. Angiography is invasive and general anesthesia is needed in most cases. Other less-invasive investigations can therefore be used to help define the group of children that need to undergo DSA. CTA has been suggested as a screening tool but its reliability is not well established (Kurian et al. 2013). Table 3 lists situations where we recommend performing DSA. We also recommend that all children who do not have their BP well controlled on two antihypertensive drugs, and where no other known diagnosis can explain the high BP, should have a formal angiogram.

Renal Doppler ultrasound may be helpful in detecting RVD in some cases, but in many cases, it is unable to detect the renal artery stenosis (Fig. 2) (Brun et al. 1997; Castelli et al. 2014;

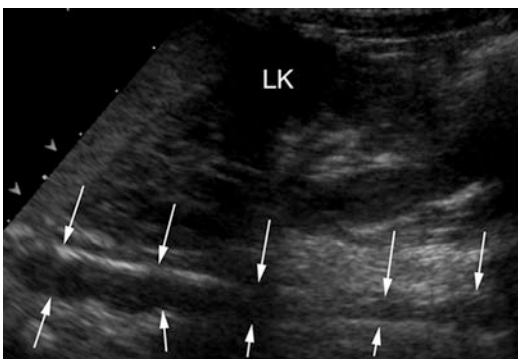
**Table 2** Diagnostic accuracy of ultrasound, pre- and post-captopril isotope studies, CTA, and MRA

Technique	Sensitivity	Specificity
US	64–85%	68–96%
Captopril renography	52–93%	63–92%
CTA	63–90%	62–97%
MRA	64–93%	72–97%

Chhadia et al. 2013; Eklof et al. 2006; Li et al. 2006). Its usefulness is however hotly debated (Brown and Karmazyn 2014). The resistive index has been used to measure blood flow in the kidneys, but the sensitivity is too low for it to definitively rule out a need for angiography (Li et al. 2006). This procedure is highly operator dependent and, even in the best hands at the present time, only has a sensitivity of 64–90% and a specificity of 68–92% (Tullus et al. 2010). In a study of 127 children from our institution, which is to be published, we found a sensitivity of Doppler US of 63% and a specificity of 96%.

**Table 3** Recommendation on when the suspicion of renal artery stenosis is strong enough to perform a formal angiography

1. Very high BP
2. Secondary symptoms of high BP including cerebral symptoms, cardiac failure, and facial palsy
3. Hypertension not controlled on  $\geq 2$  antihypertensive drugs
4. Diagnosis of a syndrome with a higher risk of vascular disease – such as neurofibromatosis and Williams syndrome
5. Signs of vasculitis in particular Takayasu disease
6. Known or suspected previous vascular insult such as renal artery thrombosis or umbilical artery catheterization
7. Transplanted kidneys
8. Bruit heard over the renal artery or arteries
9. Elevated peripheral plasma renin or moderate hypokalemia



**Fig. 2** Narrowed aorta in mid-aortic syndrome clearly shown on ultrasound

Pre- and post-captopril renal scintigraphy has been widely used to screen for RVD. This elegant idea works through the reduction of the blood flow to the kidney or part of the kidney from the treatment with the angiotensin-converting enzyme inhibitor (ACEi) (Dondi et al. 1993). This can in some cases be seen as reduced relative function of one kidney or as an uptake defect in one or both kidneys. The sensitivity (50–73%) of this investigation is, however, not good enough to make this procedure useful in clinical practice (Abdulsamea et al. 2010; Arora et al. 1997; Eklof et al. 2006; Fommei et al. 1990; Minty et al. 1993; Ng et al. 1997).

Newer imaging modalities such as computed tomography angiography (CTA) and magnetic resonance angiography (MRA) can be helpful in detecting and monitoring vascular lesions (Fig. 3). No studies on MRA or CTA exist in children with suspected RVD. The sensitivity and specificity in adult patients is between 64–93% and 64–94%, respectively (Eklof et al. 2006; Hacklander et al. 2004; Tullus et al. 2008; Vasbinder et al. 2004). Both these methods have problems with smaller blood vessels with a sensitivity of 85% in detecting clinically significant stenosis of the coronary arteries in adult patients (Miller et al. 2008). As children have even smaller blood vessels, this



**Fig. 3** MRA picture showing a narrowed aorta and a suspicion of left-sided renal artery stenosis



might be a bigger problem in the younger population. In our experience, both CTA and MRA can over- and underdiagnose RVD in children.

## Renal Vein Renins

Measurement of renal vein renin concentrations is in many cases helpful in deciding how to treat a child with RVD (Dillon and Ryness 1975; Goonasekera et al. 2002; Teigen et al. 1992). It is performed at the same time as the angiography where the femoral vein is catheterized and blood is sampled from the inferior vena cava and from both the main renal veins and their main branches. Different ratios between the renin levels in the two main renal veins or between one renal vein and the vena cava have been proposed to diagnose significant renal artery stenosis. These ratios are in our clinical experience not very helpful. We do instead assess the actual renal vein renin levels trying to define which part of the kidney(s) may be producing increased levels. This information, together with the angiographic findings, is used to prioritize which of several arterial stenoses should be treated.

## Treatment

The treatment of children with RVD should be managed by a multidisciplinary team and should be based on a combination of antihypertensive drugs, endovascular treatment with angioplasty and sometimes stenting, and surgery. Antihypertensive medications are useful in most children with RVH and are often needed as an adjunct to therapy even in children who have had successful surgery or angioplasty. It is important not to use an ACE inhibitor in these children as this very often can cause a major deterioration in the function of the affected kidney or kidneys (Wong et al. 2006). It is, in cases with unilateral renal artery stenosis, very difficult to detect deterioration of the function in that kidney with measurements of serum creatinine. The other kidney with normal blood flow will compensate for the failing kidney and keep the serum creatinine level normal or near

normal. These children will need monitoring with DMSA to follow the kidney function on both sides. Renal US can also be helpful as the kidney with impaired blood flow will show impaired growth or even shrink away. That is however a relatively late sign where there will be less reversibility if good blood flow is not reestablished.

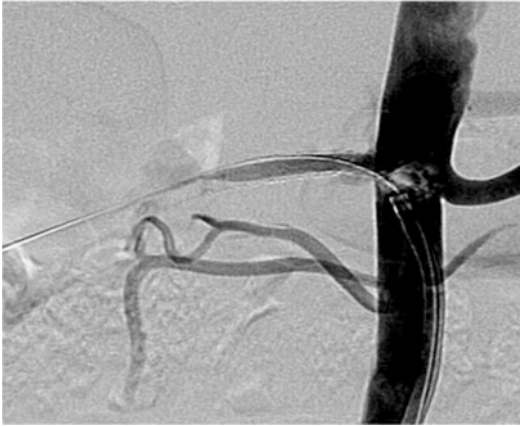
Children with active TA should be treated with immunosuppressive medication to control the inflammatory process. Many different drugs have been used including cyclophosphamide, azathioprine, mycophenolate mofetil, and TNF $\alpha$  blockers (Tullus 2013). Frequently a combination of immunosuppressive therapy and endovascular procedures will be needed to successfully treat the hypertension in patients with TA (Min et al. 2005). Endovascular therapy should preferably be reserved until the vasculitis is treated and quiescent (Tullus 2013, 2015).

## Angioplasty

It is not uncommon that children with RVD are treated with six to seven antihypertensive drugs still without effective control of their blood pressure. Angioplasty is in these cases the most commonly used treatment, and it can, with current techniques, cure or improve the blood pressure in up to 63% of children (Kari et al. 2014; Konig et al. 2006; Ladapo et al. 2015; McLaren and Roebuck 2003; Shroff et al. 2006). The artery can, in some children, after successful angioplasty, recoil and cause a residual stenosis (Eliason et al. 2016). Placement of a stent will, in such cases, help to keep the artery open (Imamura et al. 1998; Ing et al. 1995; Liang et al. 2002; Shroff et al. 2006) (Fig. 4). The lumen of the stent can, however, reduce in size with time. This can be due to intimal hyperplasia within the stent, stent thrombosis, or even stent fracture. Stents coated with antiproliferative agents like sirolimus have, in adult coronary arteries, been used to reduce the intimal hyperplasia (Palmerini et al. 2012).

Angioplasty will, in most cases, improve the blood pressure. It is important to try to understand the reason in children where that does not happen. Restenosis can cause failure of the angioplasty to

improve the blood pressure. Unfortunately many children have such widespread vascular disease that even successful treatment of some stenotic arteries is not enough. The remaining disease continues to drive the high blood pressure (Shroff et al. 2006). This can be vascular disease in the other kidney or intrarenal vascular disease that is not amenable to treatment.



**Fig. 4** Renal artery stented after angioplasty

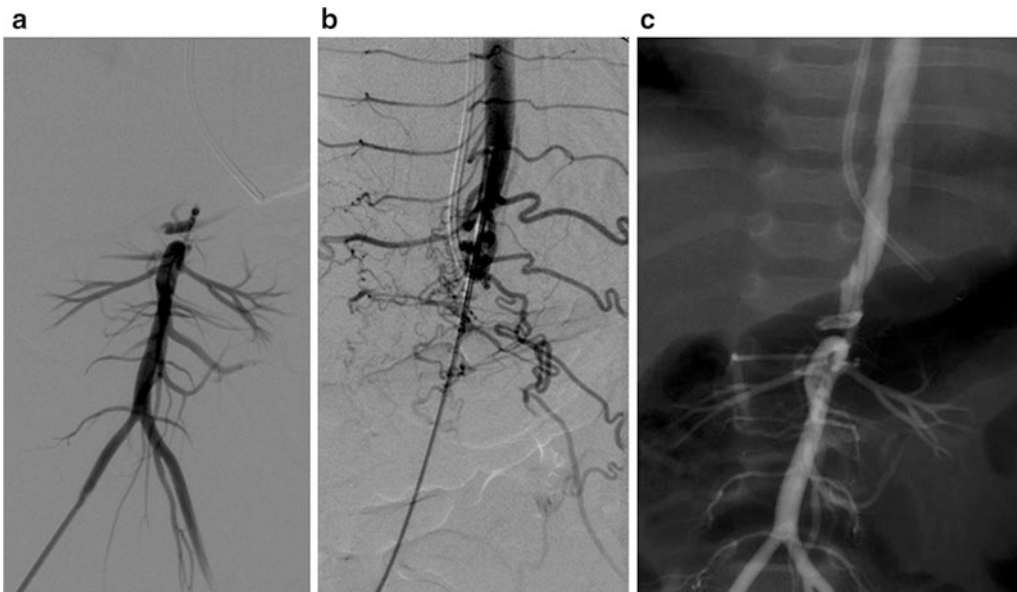
It is not uncommon that a child needs several repeat procedures to achieve an optimal result from the angioplasty (Humbert et al. 2015).

Children with severe MAS can also benefit from angioplasty. We have seen cases diagnosed with an atretic aorta that have been possible to recanalize and give the child a reasonable aorta, a normal blood pressure, and normal quality of life (Fig. 5) (Minson et al. 2012).

Some children with stenotic vascular lesions that are not amenable to angioplasty can be treated with ethanol ablation of a segment of a kidney (Ishijima et al. 1997; Teigen et al. 1992). This is particularly useful in polar arteries supplying only a small part of the kidney.

### Surgery

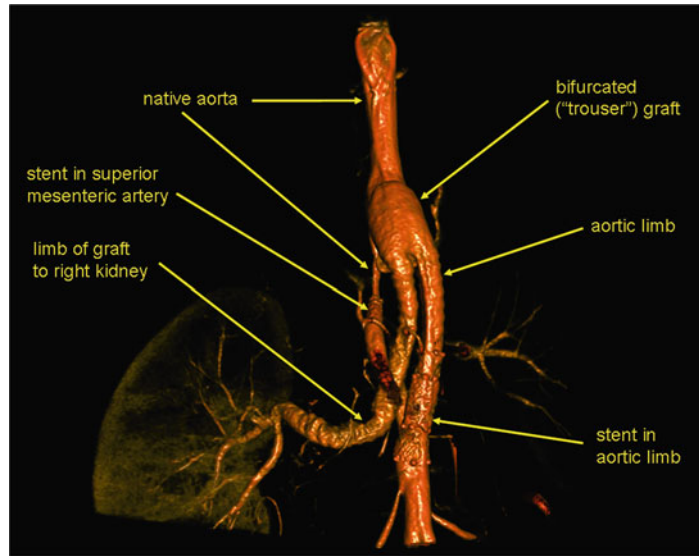
Surgery should be used in children where angioplasty has not achieved good enough blood pressure control or with aneurysmal disease which is not amenable to endovascular treatment. This assessment needs multi-professional consensus from interventional radiology, vascular surgery, and nephrology. There are many different surgical revascularization procedures. It can be performed



**Fig. 5** (a) Mid-aortic syndrome with severely narrowed aorta, no contrast passing by the narrowed part, contrast injected from below. (b) Contrast injected from above, note

collaterals. (c) After angioplasty showing an open but not normal looking aorta that functions very well

**Fig. 6** A so-called trouser graft from the upper aorta linking on to the lower aorta and right renal artery



using autologous or synthetic grafts (O'Neill, Jr. et al. 1995; Sandmann et al. 2014; Stanley et al. 2006; Stanley et al. 1995). The autologous grafts can be the splenic or the gastroduodenal artery that is pulled down to the kidney or the use of a part of the saphenous vein or internal iliac artery. Dacron is often used for the synthetic grafts (Fig. 6). The surgery on the renal arteries can sometimes be so complicated and time consuming that it needs to be done outside of the child with an ensuing autotransplantation. With very complicated pathology, e.g., stenosis of both renal arteries and MAS, a so-called trouser graft can be used. This starts from the aorta above the MAS and goes down to the aorta below the stenotic lesion and to one or both renal arteries (Fig. 6).

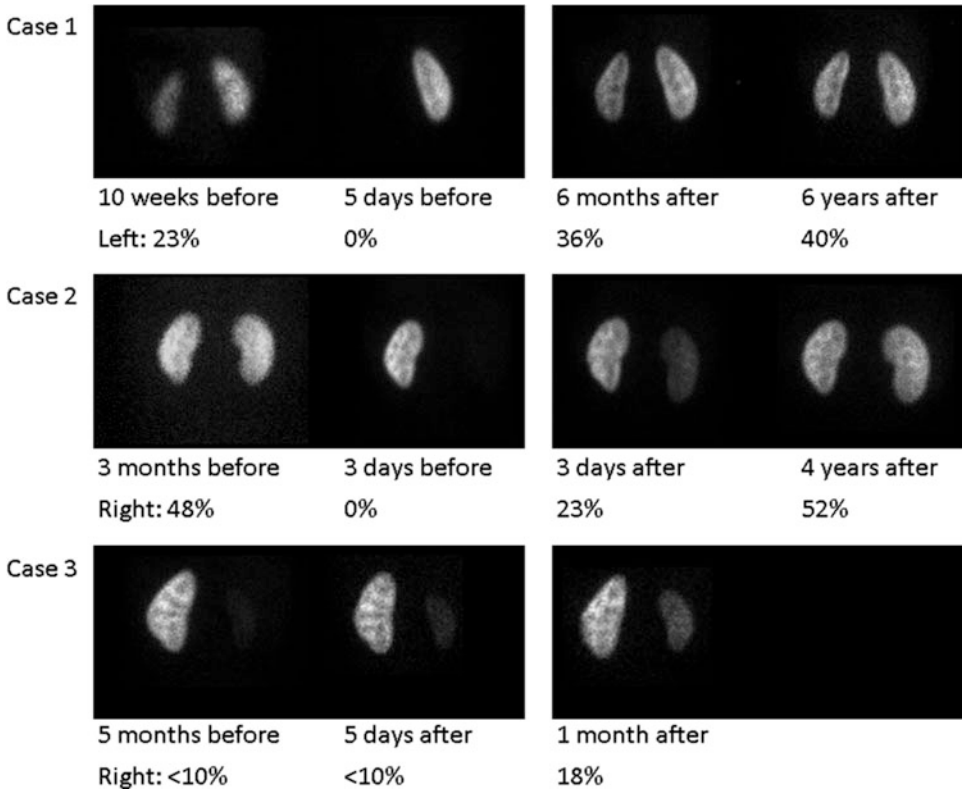
Nephrectomy can, in cases where nothing else is possible, be another surgical option. This can be very successful and cure the blood pressure in children with unilateral disease and a small non-functioning kidney (Hegde and Coulthard 2007; Tse et al. 2012). A word of caution is, however, warranted; we do sometimes see kidneys that on a pretreatment DMSA scan show less than 10% function and that after successful angioplasty or revascularization surgery recover function even up to 50% relative function (Fig. 7) (McCrinkle 1999). These kidneys do thus seem to be able to

survive on collateral circulation that does not give any meaningful kidney function as measured with DMSA. We use the size of the affected kidney measured on ultrasound to decide when to try to recover function or to go directly to nephrectomy.

With increasing experience with angioplasty, the children needing surgery have become more and more complicated. Despite this, the results of revascularization surgery are generally very good. We and other authors achieve cure or improvement of the blood pressure in up to 90% of these children (Eliason et al. 2016; Stadermann et al. 2010; Stanley et al. 2006).

### Coarctation of the Aorta

Coarctation of the aorta (CoA) accounts for a small proportion of children with high blood pressure, occurring in approximately one in 2,500 live births. It is amenable to potentially curable surgical treatment and therefore important to diagnose early (McCrinkle 1999; Walhout et al. 2008). CoA is usually diagnosed in newborn children or infants but may be detected later in life. Late presentations of CoA justify measurement of the BP in upper and lower extremities in a child of any age being evaluated for the first time for



**Fig. 7** Recovery of the kidney function as measured by DMSA after revascularization of the kidney with severely stenosed renal artery

hypertension. The classical lesion is narrowing of the aorta just below the origin of the left subclavian artery. CoA is not normally associated with narrowing of other blood vessels. The cause of hypertension is renal hypoperfusion with increased activity of the renin-angiotensin-aldosterone system (Bagby 1982; Roegel et al. 1998; Walhout et al. 2008; Yagi et al. 1968).

The presenting symptoms are mostly detection of a murmur or raised blood pressure on measurement. Some infants present with acute heart failure following the closure of the arterial duct. Later in life, many patients are asymptomatic or have more diffuse symptoms related to their increased blood pressure in the upper part of the body. Some may have symptoms related to the reduced blood flow in the legs (claudication).

Diagnosis of CoA is normally suspected clinically from the combination of higher blood

pressures in the arms compared to the legs, absent femoral pulses, and a systolic ejection murmur, which sometimes is heard better in the back. The diagnosis is confirmed with echocardiography. Angiography is still the method that best can both define anatomy and give hemodynamic data, but MRA and CTA are increasingly used (McCordle 1999).

Most of these children display signs of left ventricular hypertrophy. The optimal treatment has become controversial (Hamilton 1998). The treatment of choice used to be surgical with excision of the narrowed part of the aorta and end-to-end anastomosis. This seems to still be the preferred method in neonates and infants. In older children and in adults, balloon angioplasty is used more and more sometimes also with stenting (Wong et al. 2008). This is, however, in particular in smaller children quite controversial (Walhout et al. 2008).

Narrowing can occur also in other parts of the aorta, typically the abdominal aorta. This was previously called abdominal coarctation, but the modern preferred term is mid-aortic syndrome (MAS). MAS is in most cases related to other vascular pathology and seems in children to fall into the same spectrum as renovascular disease (see above).

The BP in children with CoA usually normalizes postsurgery. About 65% of children will, however, experience a paradoxical rise of their blood pressure in the immediate postoperative period. This can be successfully treated with a beta-blocker like propranolol or esmolol (Tabbutt et al. 2008).

A significant proportion of children will need some antihypertensive treatment after the surgery. This risk seems to increase over several decades. In one study, 30% of children with repaired CoA at a mean age of 12 years had hypertension defined by 24 h blood pressure recording. These children had their surgical repair at a mean age of 0.2 years (O'Sullivan et al. 2002). The probability of hypertension was higher in children treated at an age of more than 1 year compared to children who were treated earlier (Roegel et al. 1998; Seirafi et al. 1998). This late reoccurrence of hypertension is caused by reappearance of the stenosis in only a few children. Reduced aortic compliance and a blunted baroreceptor reflex response are other likely mechanisms (Kenny et al. 2011). The preferred method to monitor the blood pressure in these children will be with ABPM as many of them will display masked hypertension. Beta-blockade seems to be the preferred treatment of this hypertension (Kavey et al. 1990; Moltzer et al. 2010).

There are also other long-term complications after surgery for CoA; in a Danish study, 35 out of 156 patients needed cardiovascular re-interventions, 16 showed a low ejection fraction, 37 reduced exercise performance, and 33 had aneurysms in their ascending aorta or distal aortic arch. In summary only five patients had normal study findings, were normotensive, and without further intervention (Pedersen et al. 2011).

## Summary

Renovascular disease is a significant cause of severe hypertension in children, resulting from either fibromuscular dysplasia or large vessel vasculitis. Coarctation of the aorta, mid-aortic syndrome, and aneurysmal disease are less common but important differential diagnoses to consider. Doppler ultrasound is a useful screening tool; however, digital subtraction angiography is the gold standard diagnostic technique. Management decisions require multi-professional consensus from interventional radiology, vascular surgery, and nephrology. Endovascular treatment is successful in the majority of cases. Ongoing blood pressure monitoring is required given the risk of restenosis following treatment.

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## Cross-References

- ▶ [Diagnostic Evaluation of Pediatric Hypertension](#)
- ▶ [Endothelial Dysfunction and Vascular Remodeling in Hypertension](#)
- ▶ [Heritability and Familial Aggregation of Blood Pressure](#)
- ▶ [Monogenic and Polygenic Contributions to Hypertension](#)
- ▶ [Neonatal and Infant Hypertension](#)
- ▶ [Secondary Forms of Hypertension in Children: Overview](#)
- ▶ [Vascular and Cardiac Imaging Techniques and Their Applicability to Childhood Hypertension](#)
- ▶ [Vasoactive Factors and Blood Pressure in Children](#)

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Perrin C. White

## Abstract

Hypertension may be caused by abnormal synthesis of, or response to, various hormones. The proportion of pediatric hypertension cases resulting from such problems probably represents at most a few percent of cases overall, but a higher fraction of cases of severe hypertension, those occurring in the very young, or cases clustering in families. Most endocrine hypertension involves the adrenal gland and its hormones. The adrenal gland is composed of two endocrine tissues: the medulla (secreting catecholamines) and the cortex (synthesizing cortisol and aldosterone). Pheochromocytoma is mainly a disease of the adrenal medulla, although extramedullary sites may be involved. Many different diseases affecting the adrenal cortex can cause hypertension. These include hypertensive forms of congenital adrenal hyperplasia, primary aldosteronism due to hyperplasia of the zona glomerulosa or to adenomas, and Cushing's syndrome (excessive glucocorticoid exposure) due to iatrogenic etiologies, to pituitary or adrenal adenomas, or to other tumors secreting excessive ACTH. Hypertension can also be caused by thyrotoxicosis due to Graves' disease or to the thyrotoxic phase of Hashimoto's thyroiditis. It is

important to accurately diagnose these disorders because the associated hypertension requires, and usually responds well to, specific treatment of the underlying hormonal abnormality.

## Keywords

ACTH • Adrenal • Aldosterone • Catecholamines • Congenital adrenal hyperplasia • Cortisol • Cushing's syndrome • Graves' disease • Thyrotoxicosis • Thyroxine

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## Introduction

Hypertension may be caused by abnormal synthesis of, or response to, various hormones. The proportion of pediatric hypertension cases resulting

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from such problems is not known. It probably represents at most a few percent of cases overall, but a higher fraction of cases of severe hypertension, those occurring in the very young, or cases clustering in families.

## Pheochromocytoma

The vast majority of endocrine hypertension involves the adrenal gland and its hormones.

The adrenal gland is composed of two endocrine tissues: the medulla and the cortex. Pheochromocytoma is mainly a disease of the adrenal medulla although extramedullary sites may be involved.

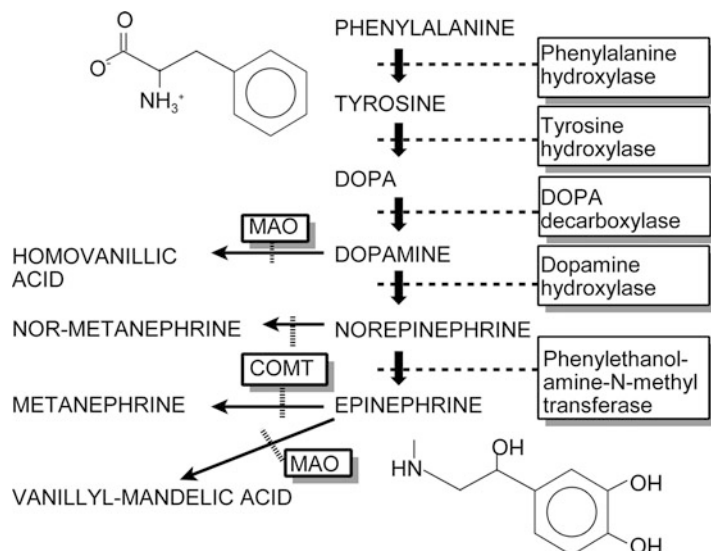
**Pathophysiology.** *Normal actions of adrenal medullary hormones.* The medulla consists mainly of neuroendocrine (chromaffin) cells and glial (sustentacular) cells with some connective tissue and vascular cells. The principal hormones of the adrenal medulla are the catecholamines dopamine, norepinephrine, and epinephrine (Fig. 1). Catecholamine synthesis also occurs in the brain, in sympathetic nerve endings, and in chromaffin tissue outside the adrenal medulla.

The effects of catecholamines are mediated through a series of G protein-coupled adrenergic receptors. Both epinephrine and norepinephrine raise mean arterial blood pressure, but only epinephrine increases cardiac output. By increasing

peripheral vascular resistance, norepinephrine increases systolic and diastolic blood pressures with only a slight reduction in the pulse rate. Epinephrine increases the pulse rate and, by decreasing peripheral vascular resistance, decreases diastolic pressure. The hyperglycemic and hypermetabolic effects of norepinephrine are much less pronounced than those of epinephrine.

*Pheochromocytomas.* Pheochromocytomas are catecholamine-secreting tumors arising from chromaffin cells in the adrenal medulla: similar tumors arising outside the adrenals are termed paragangliomas. The most common site of origin (approximately 90%) is the adrenal medulla; however, tumors may develop anywhere along the abdominal sympathetic chain and are likely to be located near the aorta at the level of the inferior mesenteric artery (the organ of Zuckerkandl) or at its bifurcation. They may also appear in the periadrenal area, urinary bladder or ureteral walls, thoracic cavity, and cervical region. They are rare in children, in whom they present most frequently between 6 and 14 years of age. Tumors vary from 1 to 10 cm in diameter; they are found more often on the right side than on the left. In more than 20% of affected children, the adrenal tumors are bilateral; in 30–40% of children, tumors are found in both adrenal and extra-adrenal areas or only in an extra-adrenal area (Turkova et al. 2016).

**Fig. 1** Biosynthesis (*right side of figure*) and metabolism (*left side of figure*) of the catecholamines norepinephrine and epinephrine. *COMT* catechol *O*-methyltransferase, *MAO* monoamine oxidase. Planar structures of phenylalanine and epinephrine are shown at the top and bottom of the figure, respectively



Pheochromocytomas may be associated with genetic syndromes such as von Hippel-Lindau disease, as a component of multiple endocrine neoplasia (MEN) syndromes MEN-2A and MEN-2B, and more rarely in association with neurofibromatosis, tuberous sclerosis, Sturge-Weber syndrome, and ataxia-telangiectasia. Mutations in the SDHB, SDHD and rarely the SDHC genes encoding subunits of the mitochondrial enzyme, succinate dehydrogenase, can cause paragangliomas, particularly at sites in the head and neck, and also pheochromocytomas. These mutations lead to intracellular accumulation of succinate, an intermediate of the Krebs cycle, which inhibits  $\alpha$ -ketoglutarate-dependent dioxygenases and results in epigenetic alterations that affect the expression of genes involved in cell differentiation (Yang et al. 2013). Fifty percent of tumors with SDHB mutations are malignant.

Germline mutations of many of these genes, particularly *VHL*, have been found in the majority of sporadic cases of pheochromocytoma in the pediatric age group (Fishbein and Nathanson 2012; Weingarten et al. 2010) (Table 1).

In addition to associations with other tumors in MEN-2 patients, pheochromocytomas and paragangliomas can occur in association with gastrointestinal stromal tumors (GISTs; the association is termed the Carney-Stratakis dyad) and/or pulmonary chondromas (Carney-Stratakis triad) and adrenocortical tumors. These associations have heterogeneous genetic etiologies but often involve mutations in SDH genes.

**Clinical manifestations.** Pheochromocytomas detected by surveillance of patients who are known carriers of mutations in tumor suppressor genes may be asymptomatic (Eisenhofer et al. 2011; Weingarten et al. 2010). Otherwise, patients are detected due to hypertension, which results from excessive secretion of epinephrine and norepinephrine. Paroxysmal hypertension is characteristic of pheochromocytoma, but in contrast to adults, the hypertension in children is more often sustained rather than paroxysmal. When paroxysms of hypertension do occur, the attacks are usually infrequent at first but become progressively more frequent until continuous hypertension supervenes. Between attacks of hypertension, the

patient may be free of symptoms. During attacks, the patient complains of headache, palpitations, abdominal pain, and dizziness; pallor, vomiting, and sweating also occur. Blood pressure may range from 180 to 260 mmHg systolic and from 120 to 210 mmHg diastolic (i.e., well above stage 2 hypertension); convulsions and other manifestations of hypertensive encephalopathy may occur. Severely hypertensive patients may complain of precordial pain and may develop pulmonary edema and cardiac and hepatic enlargement. Symptoms may be exacerbated by exercise or with the use of over-the-counter medications containing stimulants such as pseudoephedrine. Patients have a good appetite but because of the hypermetabolic state may not gain weight or grow well, and severe cachexia may develop. Polyuria and polydipsia can be sufficiently severe to suggest diabetes insipidus. Ophthalmoscopic examination may reveal papilledema, hemorrhages, exudate, and arterial constriction.

**Laboratory findings.** Pheochromocytomas produce norepinephrine and epinephrine. Normally, norepinephrine in plasma is derived from both the adrenal gland and adrenergic nerve endings, whereas epinephrine is derived primarily from the adrenal gland.

Elevated levels of free catecholamines and metanephrines are detected in plasma. In children, the best sensitivity and specificity are obtained by measuring plasma normetanephrine using gender-specific pediatric reference ranges, with plasma norepinephrine being next best (Weise et al. 2002). Plasma metanephrine and epinephrine are not reliably elevated in children. Additionally, the patient should be instructed to abstain from caffeinated drinks and to avoid acetaminophen, which can interfere with plasma normetanephrine assays. If possible, the blood sample should be obtained from an indwelling IV catheter, to avoid acute stress associated with venipuncture (Chen et al. 2010; Pacak et al. 2007).

In contrast to adults with pheochromocytoma in whom both norepinephrine and epinephrine are elevated, children with pheochromocytoma predominantly excrete norepinephrine in the urine. Total urinary catecholamine excretion usually exceeds 300  $\mu$ g/24 h. Urinary excretion of

**Table 1** Genetic causes of endocrine hypertension

Syndrome	Gene	Mutation	Protein	Functional consequence	Germline	Somatic (in tumors)
Pheochromocytoma and paraganglioma (Waguespack et al. 2010)						
Von Hippel-Lindau syndrome	VHL	Inactivating	VHL protein is an E3 ubiquitin ligase (which targets hypoxia-inducible factors for proteolysis)	Loss of tumor suppressor gene	+	+
Multiple endocrine neoplasia 2A/B	RET	Activating	RET protein is a receptor tyrosine kinase	Activated proto-oncogene	+	+
Neurofibromatosis	NF-1	Inactivating	Neurofibromin-1 (GTPase-activating protein; inhibits proliferative growth by blocking RAS-mediated signaling)	Loss of tumor suppressor gene	+	
Familial paragangliomas (PGL1)	SDHD	Inactivating	Succinate dehydrogenase subunit D (membrane-anchorage)	Accumulation of succinate leads to oncogenic epigenetic changes	+	+
PGL2	SDH5/SDHAF2	Inactivating	Succinate dehydrogenase flavinylation factor (promotes assembly of enzyme complex)	Accumulation of succinate leads to oncogenic epigenetic changes	+	+
PGL3	SDHC	Inactivating	Succinate dehydrogenase subunit C (ubiquinone binding)	Accumulation of succinate leads to oncogenic epigenetic changes	+	+
PGL4	SDHB	Inactivating	Succinate dehydrogenase subunit B (catalytic)	Accumulation of succinate leads to oncogenic epigenetic changes	+	+
Hypertensive forms of congenital adrenal hyperplasia (Auchus 2001; White 2001)						
11 $\beta$ -Hydroxylase deficiency	CYP11B1	Inactivating	Steroid 11 $\beta$ -hydroxylase	Inability to synthesize cortisol leads to elevated levels of deoxycorticosterone	+	
17 $\alpha$ -Hydroxylase deficiency	CYP17A1	Inactivating	Steroid 17 $\alpha$ -hydroxylase	Inability to synthesize cortisol leads to elevated levels of deoxycorticosterone	+	
Apparent mineralocorticoid excess (White et al. 1997)						
	HSD11B2	Inactivating	11 $\beta$ -Hydroxysteroid dehydrogenase 2	Cortisol activates the mineralocorticoid receptor	+	

(continued)

**Table 1** (continued)

Syndrome	Gene	Mutation	Protein	Functional consequence	Germline	Somatic (in tumors)
Primary aldosteronism (Vaidya et al. 2015)						
Glucocorticoid-suppressible hyperaldosteronism	Chimeric CYP11B1/CYP11B2	Activating	Aldosterone synthase	CYP11B2 is expressed at high levels and regulated by ACTH	+	
Familial hyperaldosteronism	KCNJ5	Activating	Inwardly rectifying potassium channel	Increases Na <sup>+</sup> conductance, depolarizes cell, opens voltage-sensitive calcium channel, which increases intracellular calcium and thus CYP11B2 expression	+	+
Familial hyperaldosteronism	CACNA1D	Activating	Voltage-sensitive calcium channel	Opens channel, increasing intracellular calcium and thus CYP11B2 expression	+	+
Aldosterone-producing adenomas	ATP1A1	Inactivating	Na <sup>+</sup> /K <sup>+</sup> ATPase	Reduces pump activity, lower depolarization threshold		+
Aldosterone-producing adenomas	ATP2B3	Inactivating	Calcium ATPase	Intracellular calcium accumulation		+
Adrenal Cushing's syndrome (Lodish and Stratakis 2016)						
McCune-Albright syndrome	GNAS	Activating	G <sub>s</sub> stimulatory G protein subunit	Activates adenylyl cyclase in all cells expressing the abnormal G protein; constitutive activation of cAMP-mediated signaling pathway		+
Carney complex (including primary pigmented nodular adrenocortical disease (PPNAD))	PRKAR1A	Inactivating	Regulatory subunit of protein kinase A	Constitutive activation of cAMP-mediated signaling pathway	+	+
Primary bilateral macronodular adrenal hyperplasia (PBMAH)	PRKACA	Increased copy number	Catalytic subunit of protein kinase A	Constitutive activation of cAMP-mediated signaling pathway	+	+
Cortisol-secreting adenomas	PRKACA	Activating	Catalytic subunit of protein kinase A	Constitutive activation of cAMP-mediated signaling pathway		+

(continued)

**Table 1** (continued)

Syndrome	Gene	Mutation	Protein	Functional consequence	Germline	Somatic (in tumors)
PPNAD	PDE8B, PDE11A	Inactivating	Phosphodiesterase	Increases intracellular levels of cAMP; constitutive activation of cAMP-mediated signaling pathway	+	
Multiple endocrine neoplasia type 1 (PBMAH)	MEN1	Inactivating	Menin	Loss of tumor suppressor gene	+	+
PBMAH	ARMC5	Inactivating	Armadillo repeat-containing protein 5	Loss of tumor suppressor gene	+	+
Generalized glucocorticoid resistance (Charmandari et al. 2013)						
	NR3C1	Inactivating	Glucocorticoid receptor	Insensitivity to cortisol leads to elevated levels of deoxycorticosterone	+	

metanephrines (particularly normetanephrine) is also increased (Eisenhofer et al. 2013; Weingarten et al. 2010). Daily urinary excretion of these compounds by unaffected children increases with age. Although urinary excretion of vanillylmandelic acid (VMA, 3-methoxy-4-hydroxymandelic acid), the major metabolite of epinephrine and norepinephrine, is increased, vanilla-containing foods and fruits can produce falsely elevated levels of this compound, which therefore is no longer routinely measured. In general, urinary catecholamine testing has lower sensitivity but higher specificity than plasma testing; of course, it may also be relatively difficult to obtain a reliable 24-h specimen in young children.

Most tumors in the area of the adrenal gland are readily localized by CT or MRI, but extra-adrenal tumors may be difficult to detect. <sup>131</sup>I-metaiodobenzylguanidine (MIBG) is taken up by chromaffin tissue anywhere in the body and is useful for localizing small tumors (Derlin et al. 2013; Ilias et al. 2011). Venous catheterization with sampling of blood at different levels for catecholamine determinations is now only rarely necessary for localizing the tumor.

**Differential diagnosis.** Various causes of hypertension in children must be considered, such as renal or renovascular disease, coarctation of the aorta, other forms of endocrine

hypertension discussed in this chapter, and primary hypertension. A nonfunctioning kidney may result from compression of a ureter or of a renal artery by a pheochromocytoma. Paroxysmal hypertension may be associated with porphyria or familial dysautonomia. Cerebral disorders, diabetes insipidus, diabetes mellitus, and hyperthyroidism must also be considered in the differential diagnosis. Hypertension in patients with neurofibromatosis may be caused by renal vascular involvement or by concurrent pheochromocytoma (Zinnamosca et al. 2011).

Neuroblastomas, ganglioneuroblastomas, and ganglioneuromas frequently produce catecholamines, but urinary levels of most catecholamines are higher in patients with pheochromocytoma, although levels of dopamine and homovanillic acid are usually higher in neuroblastoma. Secreting neurogenic tumors often cause hypertension, excessive sweating, flushing, pallor, rash, polyuria, polydipsia, and – particularly with ganglioneuroma – chronic diarrhea.

**Treatment.** Pheochromocytomas must be removed surgically (Chen et al. 2010; Pacak et al. 2007). Because these tumors are often multiple in children, a thorough transabdominal exploration of all the usual sites offers the best opportunity to find them all. Manipulation and excision of these tumors result in marked

increases in catecholamine secretion that increase blood pressure and heart rate. Therefore preoperative  $\alpha$ - and  $\beta$ -adrenergic blockade are required (Donckier and Michel 2010; Luiz et al. 2016; Weingarten et al. 2010). The recommended approach is to produce complete alpha blockade with either phenoxybenzamine or doxazosin before adding beta-blockade. Blood volume must be expanded with appropriate fluids before and during surgery to avoid a precipitous drop in blood pressure during the operation or within 48 h postoperatively.

Although these tumors often appear malignant histologically, in general the only accurate indicators of malignancy are the presence of metastatic disease, local invasiveness that precludes complete resection, or both (Ayala-Ramirez et al. 2011). Approximately 10% of all adrenal pheochromocytomas are malignant, but such tumors are rare in childhood. Malignant pheochromocytomas occur more frequently in extra-adrenal sites – particularly the mediastinum and the infradiaphragmatic para-aortic area, including the organ of Zuckerkandl – and are often associated with mutations in the SDHB gene encoding a subunit of succinate dehydrogenase (Dannenberget al. 2005; Erlic et al. 2009). Large tumors are more likely to be malignant, particularly in individuals with SDHB mutations (Ayala-Ramirez et al. 2011; Schovaneck et al. 2014; Waguespack et al. 2010).

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## Diseases of the Adrenal Cortex Causing Hypertension

**Physiology.** The adrenal cortex consists of three concentric zones: the zona glomerulosa outermost, then the zona fasciculata (which comprises around three fourths of the cortex), and finally the zona reticularis, lying next to the adrenal medulla. The zona glomerulosa synthesizes aldosterone, the most potent mineralocorticoid. The zona fasciculata produces cortisol, and the zona fasciculata and zona reticularis synthesize adrenal androgens.

*Adrenal steroidogenesis.* Cholesterol is the starting substrate for all steroid biosynthesis (Fig. 2) (Miller and Auchus 2011). In

mitochondria, the side chain of cholesterol is cleaved to yield pregnenolone, which then diffuses out of the mitochondria and enters the endoplasmic reticulum. The subsequent reactions that occur depend on the zone of the adrenal cortex.

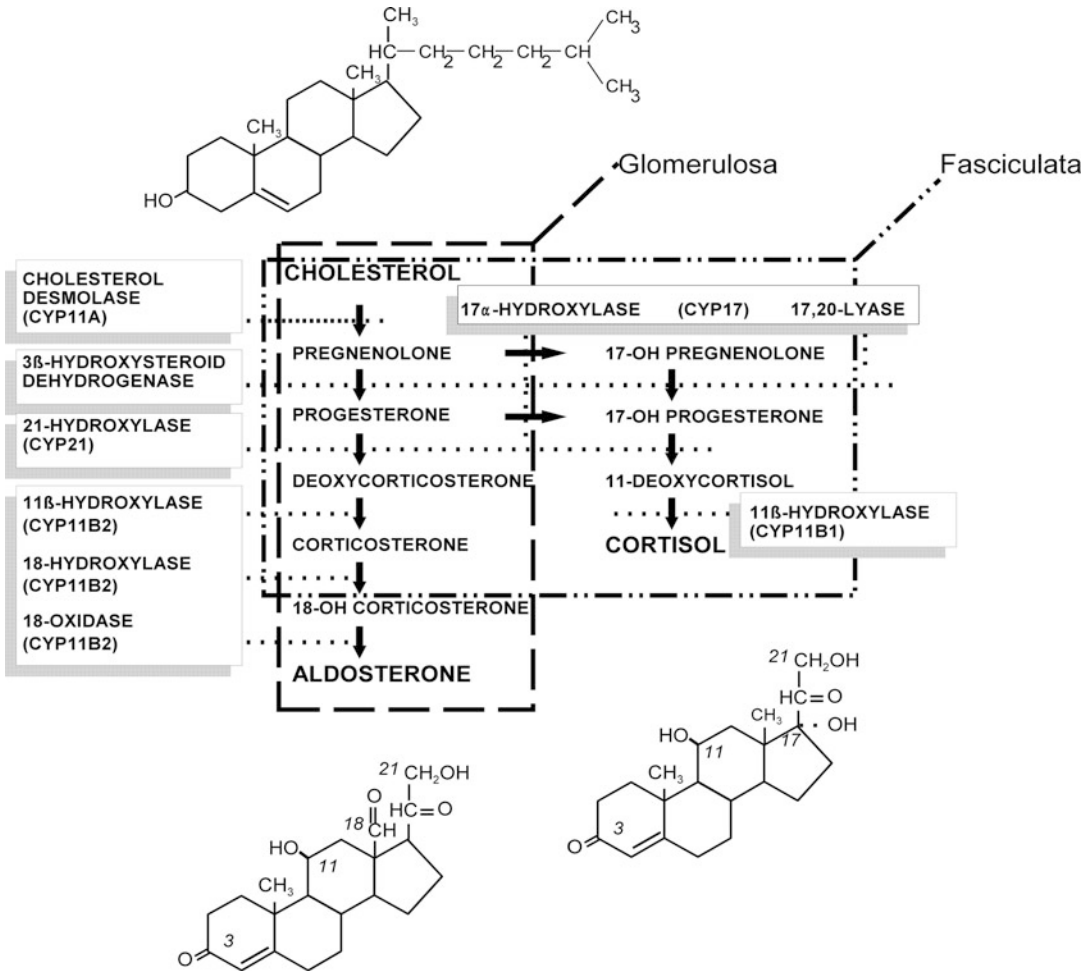
In the zona glomerulosa, pregnenolone is successively converted to progesterone and 11-deoxycorticosterone. Deoxycorticosterone then reenters mitochondria and is converted to aldosterone by aldosterone synthase (P450aldo, CYP11B2), a P450 enzyme which carries out three successive oxidations: 11 $\beta$ -hydroxylation, 18-hydroxylation, and further oxidation of the 18-methyl carbon to an aldehyde (Curnow et al. 1991).

In the endoplasmic reticulum of the zona fasciculata, pregnenolone is converted by 17 $\alpha$ -hydroxylase (P450c17, CYP17) to 17-hydroxypregnenolone. This enzyme is not expressed in the zona glomerulosa, which consequently cannot synthesize 17-hydroxylated steroids. 17-hydroxypregnenolone is converted to 17-hydroxyprogesterone and then 11-deoxycortisol which finally reenters mitochondria and is converted to cortisol by steroid 11- $\beta$ -hydroxylase (P450c11, CYP11B1). This enzyme is closely related to aldosterone synthase but has low 18-hydroxylase and nonexistent 18-oxidase activity (Curnow et al. 1991). Thus, under normal circumstances, the zona fasciculata cannot synthesize aldosterone.

*Regulation of cortisol secretion.* Glucocorticoid secretion is regulated mainly by adrenocorticotrophic hormone (corticotropin, ACTH), which is secreted by the anterior pituitary gland in pulses which vary diurnally in amplitude. Pulses of ACTH and cortisol are highest at about the time of waking, are low in late afternoon and evening, and reach their lowest point 1 or 2 h after sleep begins.

ACTH acts through a specific G protein-coupled receptor (also termed the melanocortin receptor-2, encoded by the *MCR2* gene) to activate adenylate cyclase and increase levels of cyclic adenosine monophosphate (cAMP) (Clark and Metherell 2006). Cyclic AMP has short-term (minutes to hours) effects on cholesterol transport into mitochondria by increasing expression of





**Fig. 2** Adrenal steroid biosynthesis. Reactions occurring in the zonae glomerulosa and fasciculata are enclosed by labeled dotted lines; several reactions take place in both zones. Many of the involved enzymes are cytochromes P450 (CYP). CYP11B2 mediates successive 11 $\beta$ -hydroxylase, 18-hydroxylase, and 18-oxidase

reactions in the zona glomerulosa for the conversion of deoxycorticosterone to aldosterone. Planar structures of cholesterol, aldosterone, and cortisol are illustrated; relevant carbon positions on the latter two molecules are marked

steroidogenesis acute regulatory (StAR) protein (Stocco 2001). The long-term effects (hours to days) of ACTH stimulation are to increase the uptake of cholesterol and the expression of genes encoding the enzymes required to synthesize cortisol.

*Regulation of aldosterone secretion.* The rate of aldosterone synthesis, which is normally 100- to 1,000-fold less than that of cortisol synthesis, is regulated mainly by the renin-angiotensin-aldosterone system (RAAS) and by potassium levels, with ACTH having only a short-term effect. In

response to decreased intravascular volume, renin is secreted by the juxtaglomerular apparatus of the kidney. Renin is a proteolytic enzyme that cleaves angiotensinogen (renin substrate), an  $\alpha_2$ -globulin produced by the liver, to yield the inactive decapeptide angiotensin I. Angiotensin-converting enzyme in the lungs and other tissues rapidly cleaves angiotensin I to the biologically active octapeptide angiotensin II. Cleavage of angiotensin II produces the heptapeptide angiotensin III. Angiotensins II and III are potent stimulators of aldosterone secretion; angiotensin II is a more potent

vasopressor agent. Angiotensins II and III occupy a G protein-coupled receptor activating phospholipase C (Higuchi et al. 2007). The latter protein hydrolyzes phosphatidylinositol bisphosphate to produce inositol trisphosphate and diacylglycerol, which raise intracellular calcium levels and activate protein kinase C and calmodulin-activated (CaM) kinases (Condon et al. 2002). Similarly, increased levels of extracellular potassium depolarize the cell membrane and increase calcium influx through voltage-gated L-type calcium channels. Phosphorylation of transcriptional regulatory factors by CaM kinases increases transcription of the aldosterone synthase (CYP11B2) enzyme required for aldosterone synthesis (Bassett et al. 2004; Nogueira and Rainey 2010).

*Adrenal steroid hormone actions.* Aldosterone and cortisol act through distinct receptors that belong to a larger superfamily of nuclear transcriptional factors. Hormone molecules diffuse through the cell membrane and bind to these receptors, changing their conformation and causing them to bind DNA at specific hormone response elements. Bound receptors may recruit other transcriptional co-regulatory factors to DNA.

The responses to each hormone are determined by the different genes that are regulated by the hormone in different tissues. Additionally, different combinations of co-regulators are expressed in different tissues, allowing each steroid hormone to have many different effects. Moreover, enzymes may increase or decrease the affinity of steroids for their receptors and thus modulate their activity. For example, 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (HSD11B1) converts cortisone, which is not a ligand for the glucocorticoid receptor, to cortisol, which is an active glucocorticoid (Tomlinson and Stewart 2005). This increases local glucocorticoid concentrations in several tissues, especially the liver. Conversely, 11 $\beta$ -hydroxysteroid dehydrogenase type 2 (HSD11B2) oxidizes cortisol to cortisone, particularly in the kidney, preventing mineralocorticoid receptors from being occupied by high levels of cortisol (Mune et al. 1995; White et al. 1997) (see ► [Chap. 7, “Monogenic and Polygenic Contributions to Hypertension”](#) and below).

*Actions of glucocorticoids.* The term glucocorticoid refers to the glucose-regulating properties of these hormones. However, glucocorticoids such as cortisol have many other effects, including actions on circulatory and renal function, that may contribute to the development of hypertension.

Glucocorticoids have a positive inotropic influence on the heart, increasing the left ventricular work index (Santos and Spadari-Bratfisch 2006). Moreover, they have a permissive effect on the actions of epinephrine and norepinephrine on both the heart and the blood vessels (Yang and Zhang 2004). In the absence of glucocorticoids, decreased cardiac output and shock may develop; in states of glucocorticoid excess, hypertension is frequently observed. This may be due in part to the activation of the mineralocorticoid receptor (see later), which occurs when renal 11 $\beta$ -hydroxysteroid dehydrogenase is saturated by excessive levels of glucocorticoids.

*Actions of mineralocorticoids.* The most important mineralocorticoids are aldosterone and, to a lesser degree, 11-deoxycorticosterone; corticosterone and cortisol are normally not important as mineralocorticoids unless secreted in excess. Mineralocorticoids maintain intravascular volume by conserving sodium and eliminating potassium and hydrogen ions. They exert these actions in the kidney, gut, and salivary and sweat glands (Tomaschitz et al. 2010). Aldosterone may have distinct effects in other tissues. Mineralocorticoid receptors are found in the heart and vascular endothelium, and aldosterone increases myocardial fibrosis in heart failure (Funder 2001).

Mineralocorticoids have their most important actions in the distal convoluted tubules and cortical collecting ducts of the kidney, where they induce reabsorption of sodium and secretion of potassium. In the medullary collecting duct, they act in a permissive fashion to allow vasopressin to increase osmotic water flux (Tomaschitz et al. 2010). Thus, patients with mineralocorticoid excess may develop hypertension, hypokalemia, and metabolic alkalosis.

The mechanisms by which aldosterone affects sodium excretion are incompletely understood. Most effects of aldosterone are presumably due

to changes in gene expression mediated by the mineralocorticoid receptor, and indeed levels of subunits of both the  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase and the epithelial sodium channel (ENaC) increase in response to aldosterone. Additionally, aldosterone increases expression of the serum- and glucocorticoid-regulated kinase (SGK), which indirectly reduces turnover of ENaC subunits and thus increases the number of open sodium channels (Soundararajan et al. 2010) (see also ► Chap. 7, “Monogenic and Polygenic Contributions to Hypertension”).

The mineralocorticoid receptor has similar affinities in vitro for cortisol and aldosterone, yet cortisol is a weak mineralocorticoid in vivo. This discrepancy results from the action of 11- $\beta$ -hydroxysteroid dehydrogenase type 2, which converts cortisol to cortisone. Cortisone is not a ligand for the receptor, whereas aldosterone is not a substrate for the enzyme. Pharmacologic inhibition or genetic deficiency of this enzyme allows cortisol to occupy renal mineralocorticoid receptors and produce sodium retention and hypertension. Pharmacologic inhibition is most often caused by excessive licorice ingestion (the active compounds are glycyrrhizic acid and glycyrrhetic acid) or licorice-flavored chewing tobacco; the genetic condition is termed apparent mineralocorticoid excess syndrome (Mune et al. 1995; White et al. 1997) (see ► Chap. 7, “Monogenic and Polygenic Contributions to Hypertension”).

## Hypertensive Forms of Congenital Adrenal Hyperplasia

**Congenital adrenal hyperplasia due to 11 $\beta$ -hydroxylase deficiency.** Deficiency of 11 $\beta$ -hydroxylase is caused by mutations in the *CYP11B1* gene located on chromosome 8q24 (Curnow et al. 1993; White 2001). Its incidence has been estimated to be 1/250,000–1/100,000. *CYP11B1* mediates 11-hydroxylation of 11-deoxycortisol to cortisol. Because 11-deoxycortisol is not converted to cortisol, levels of corticotropin are high. In consequence, precursors accumulate and are shunted into androgen biosynthesis, so that females may be born

with ambiguous genitalia. However, the adjacent *CYP11B2* gene encoding aldosterone synthase is generally unaffected in this disorder, so patients are able to synthesize aldosterone normally. Plasma levels of 11-deoxycortisol and deoxycorticosterone are elevated. Because deoxycorticosterone and metabolites have mineralocorticoid activity, plasma renin activity is suppressed. Consequently, aldosterone levels are low, even though the ability to synthesize aldosterone is intact. Approximately two thirds of patients become hypertensive, although this can take several years to develop. Hypokalemic alkalosis occasionally occurs.

**Congenital adrenal hyperplasia due to 17-hydroxylase deficiency.** This is a very rare disorder caused by mutations in the *CYP17* gene (Auchus 2001). The encoded enzyme catalyzes two distinct reactions: 17-hydroxylation of pregnenolone and progesterone to 17-hydroxypregnenolone and 17-hydroxyprogesterone, respectively, and the 17,20-lyase reaction mediating conversion of 17-hydroxypregnenolone to dehydroepiandrosterone. The enzyme is expressed in both the adrenal cortex and the gonads. Most mutations affect both the hydroxylase and lyase activities.

Patients with 17-hydroxylase deficiency cannot synthesize cortisol, but their ability to synthesize corticosterone is intact. Because corticosterone is an active glucocorticoid, patients do not develop adrenal insufficiency. Deoxycorticosterone, the immediate precursor of corticosterone, is synthesized in excess. This can cause hypertension, hypokalemia, and suppression of renin and aldosterone secretion, as occurs in 11-hydroxylase deficiency. However, in contrast to 11-hydroxylase deficiency, patients with 17-hydroxylase deficiency are unable to synthesize sex hormones. Affected males are incompletely virilized and present as phenotypic females (but gonads are usually palpable in the inguinal region or the labia) or with sexual ambiguity. Affected females usually present with failure of sexual development at the expected time of puberty.

**Treatment.** Patients are treated with hydrocortisone in doses of 15–20 mg/M<sup>2</sup>/day. Hypertension often resolves with glucocorticoid treatment but may require additional therapy, especially if it has been long standing. Calcium channel blockers

may be beneficial under these circumstances. Additionally, females with 17-hydroxylase deficiency require estrogen replacement at puberty, whereas genetic males with this condition may require either estrogen or androgen supplementation depending on the sex of rearing.

## Primary Aldosteronism

**Clinical manifestations.** Primary aldosteronism encompasses disorders caused by excessive aldosterone secretion independent of the RAAS. These disorders are characterized by hypertension, hypokalemia, and suppression of the RAAS. The three main etiologies are aldosterone-secreting adenomas, bilateral micronodular adrenocortical hyperplasia, and glucocorticoid-suppressible (or glucocorticoid-remediable) aldosteronism.

Aldosterone-secreting adenomas are usually unilateral and have been reported in children as young as 3.5 years of age. Bilateral micronodular adrenocortical hyperplasia tends to occur in older children. Primary aldosteronism due to unilateral adrenal hyperplasia may also occur.

Glucocorticoid-suppressible aldosteronism (also discussed in ► Chap. 7, “Monogenic and Polygenic Contributions to Hypertension”) is an autosomal dominant form of low-renin hypertension in which aldosterone secretion is rapidly suppressed by glucocorticoid administration, suggesting that it is regulated by ACTH instead of the renin-angiotensin system. The disorder is caused by unequal meiotic crossing over events between the adjacent *CYP11B1* (11 $\beta$ -hydroxylase) and *CYP11B2* (aldosterone synthase) genes, which produces a third chimeric gene with regulatory sequences of *CYP11B1* juxtaposed with coding sequences of *CYP11B2* (Lifton et al. 1992; Pascoe et al. 1992). This results in the inappropriate expression of a *CYP11B2*-like enzyme with aldosterone synthase activity in the adrenal fasciculata.

These conditions are thought to be rare in children, but they may account for 5–10% of cases of hypertension in adults (Vaidya et al. 2015). Although adenomas and bilateral hyperplasia are usually sporadic, kindreds with several affected members have been reported. Genetic linkage to

chromosome 7p22 has been identified in some of these kindreds, but the involved gene has not yet been identified. On the other hand, mutations have been identified in several components of the mechanism by which potassium regulates aldosterone secretion (see *Regulation of aldosterone secretion*, above). Germline mutations in the *KCNJ5* gene on chromosome 11q24 have been identified in several kindreds; these mutations alter potassium channel selectivity, producing increased Na<sup>+</sup> conductance and membrane depolarization, which increases aldosterone production and proliferation of adrenal glomerulosa cells (Scholl et al. 2012). Moreover, somatic mutations in the same gene have been identified in a subset of sporadic aldosterone-producing adenomas (Choi et al. 2011). Germline and somatic mutations have also been reported in the *CACNA1D* gene encoding a voltage-sensitive calcium channel, and somatic mutations in *ATP1A1* and *ATP2B3*, respectively, encoding sodium-potassium and calcium ATPases (Vaidya et al. 2015).

Some affected children have no symptoms, the diagnosis being established after incidental discovery of moderate hypertension. Others may have severe hypertension (up to 240/150 mmHg), with headache, dizziness, and visual disturbances.

**Laboratory findings.** Hypokalemia occurs often but not invariably; it is exacerbated by thiazide diuretics. Chronic hypokalemia may lead to polyuria, nocturia, enuresis, and polydipsia. Muscle weakness and discomfort, intermittent paralysis, fatigue, and growth failure affect children with severe hypokalemia.

Serum pH and the carbon dioxide and sodium concentrations may be elevated and the serum chloride and magnesium levels decreased. Serum levels of calcium are normal. Plasma levels of aldosterone may be normal or elevated. Aldosterone concentrations in 24-h urine collections are always increased. Plasma levels of renin are consistently low. The ratio of plasma aldosterone concentration to renin activity is always high, and this represents a cost-effective screening test for primary aldosteronism (Stowasser et al. 2012). However, both renin and aldosterone levels may vary by time of day, posture, and sodium intake,

making it difficult to establish consistent reference ranges. Moreover, aldosterone/renin ratios tend to be lower in normotensive children than in adults (Martinez-Aguayo et al. 2010). Therefore, a consistent sampling protocol should be used – for example, mid-morning after the patient has been sitting for 15 min. If possible, antihypertensive drugs or other medications that can affect aldosterone or renin secretion should be avoided for several weeks prior to testing, including diuretics,  $\beta$ -blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, clonidine, and nonsteroidal anti-inflammatory agents. Calcium channel blockers have smaller effects on the biochemical measurements.

Urinary and plasma levels of 18-oxocortisol and 18-hydroxycortisol – 17-hydroxylated homologs of aldosterone and 18-hydroxycorticosterone, respectively – are markedly increased in glucocorticoid-suppressible aldosteronism and to a lesser extent in other forms of primary aldosteronism.

Primary aldosteronism should be distinguished from glucocorticoid-suppressible aldosteronism, which is specifically treated with glucocorticoids. An autosomal dominant pattern of inheritance should raise suspicion for the latter disorder. Glucocorticoid-suppressible aldosteronism is diagnosed by dexamethasone suppression tests or by specific genetic testing (see ► Chap. 7, “Monogenic and Polygenic Contributions to Hypertension”).

Provocative testing may increase the accuracy of diagnosis of primary aldosteronism; aldosterone will not decrease with administration of saline solution or fludrocortisone. Selective adrenal vein sampling may establish whether the abnormal aldosterone secretion is originating from one or both adrenals and thus distinguish between adenomas and bilateral hyperplasia. MRI may detect an adenoma but should be interpreted cautiously (particularly in adults) because adrenal incidentalomas are not uncommon (in adults) and can confuse the diagnosis (Funder et al. 2008; Nishikawa et al. 2011).

**Treatment.** The treatment of an aldosterone-producing adenoma is surgical removal. Aldosteronism due to bilateral adrenal hyperplasia is

treated with the mineralocorticoid antagonists spironolactone or eplerenone, often normalizing blood pressure and serum potassium levels. There is greater experience with spironolactone, but this agent has antiandrogenic properties that may be unacceptable in pubertal males. Eplerenone is a more specific anti-mineralocorticoid that is safe and effective in children with hypertension, but has not been examined specifically in those with aldosteronism (Li et al. 2010). As an alternative, an epithelial sodium channel blocker such as amiloride may be used and other antihypertensive agents, such as calcium channel blockers, added as necessary (Funder et al. 2008; Nishikawa et al. 2011; Steichen et al. 2012).

Glucocorticoid-suppressible aldosteronism is managed by daily administration of a glucocorticoid, usually dexamethasone, 25  $\mu\text{g}/\text{kg}/\text{day}$  in divided doses. Hypertension resolves in patients in whom the hypertension is not severe or of long standing. If necessary, additional antihypertensive medications may be used, such as spironolactone or eplerenone.

## Cushing’s Syndrome

**Pathophysiology.** Cushing’s syndrome is the result of abnormally high blood levels of cortisol or other glucocorticoids. This can be iatrogenic or the result of endogenous cortisol secretion, due either to an adrenal tumor or to hypersecretion of corticotropin (adrenocorticotrophic hormone [ACTH]) by the pituitary (Cushing’s disease) or by a tumor.

The most common cause of Cushing’s syndrome is prolonged exogenous administration of glucocorticoid hormones, especially at the high doses used to treat lymphoproliferative disorders. Endogenous Cushing’s syndrome in infants and young children is most often caused by a functioning adrenocortical tumor. Patients with these tumors often exhibit signs of hypercortisolism along with signs of hypersecretion of other steroids such as androgens, estrogens, and aldosterone.

Although extremely rare in infants, the most common etiology of endogenous Cushing’s

syndrome in children older than 7 years of age is Cushing's disease, in which excessive ACTH secreted by a pituitary adenoma causes bilateral adrenal hyperplasia. Such adenomas are often too small to detect by imaging techniques and are termed microadenomas. ACTH-dependent Cushing's syndrome may also result from ectopic production of ACTH, although this is uncommon in children. Ectopic ACTH secretion in children has been associated with islet cell carcinoma of the pancreas, neuroblastoma or ganglioneuroblastoma, hemangiopericytoma, Wilms tumor, and thymic carcinoid. Hypertension is more common in the ectopic ACTH syndrome than in other forms of Cushing's syndrome, because very high cortisol levels may overwhelm 11 $\beta$ -hydroxysteroid dehydrogenase type 2 in the kidney and thus have an enhanced mineralocorticoid (salt-retaining) effect.

Several syndromes are associated with the development of multiple autonomously hyperfunctioning nodules of adrenocortical tissue, rather than single adenomas or carcinomas. In many cases they are caused by mutations in genes in the cAMP-mediated signaling pathway by which ACTH normally regulates cortisol secretion. ACTH-independent Cushing's syndrome with nodular hyperplasia and adenoma formation occurs rarely in cases of McCune-Albright syndrome, with symptoms beginning in infancy or childhood. McCune-Albright syndrome is caused by a somatic mutation of the *GNAS* gene encoding the G protein, G $\alpha$ , through which the ACTH receptor (MCR2) normally signals. This results in constitutive activation of adenylate cyclase, thus increasing levels of cyclic adenosine monophosphate (cAMP). When the mutation is present in adrenal tissue, cortisol and cell division are stimulated independently of ACTH. Other tissues in which activating mutations may occur are the bone (producing fibrous dysplasia), gonads, thyroid, and pituitary. Clinical manifestations depend on which tissues are affected.

Primary pigmented nodular adrenocortical disease (PPNAD) is a distinctive form of ACTH-independent Cushing's syndrome. It may occur as an isolated event or, more commonly, as a familial disorder with other manifestations. The adrenal glands have characteristic multiple, small

(<4 mm in diameter), pigmented nodules containing large cells with cytoplasm and lipofuscin; there is cortical atrophy between the nodules. This adrenal disorder occurs as a component of Carney complex, an autosomal dominant disorder also consisting of centropalpebral lentiginosities and blue nevi; cardiac and cutaneous myxomas; pituitary, thyroid, and testicular tumors; and pigmented melanotic schwannomas. Carney complex is inherited in an autosomal dominant manner, although sporadic cases occur. Many cases are caused by inactivating mutations in the gene for the type 1 $\alpha$  regulatory subunit of protein kinase A (PRKAR1A) on chromosome 17q22–24 (Kirschner et al. 2000). Patients with Carney complex and PRKAR1A mutations generally develop PPNAD as adults. Conversely, children presenting with PPNAD as an isolated finding rarely have mutations in PRKAR1A, or subsequently develop other manifestations of Carney complex. Some patients with isolated PPNAD have mutations in the PDE8B (Horvath et al. 2008) or PDE11A (Horvath et al. 2006) genes encoding different phosphodiesterase isozymes; these increase intracellular levels of cAMP. In contrast, activating somatic mutations (particularly Leu206Arg) have been documented in the PRKACA catalytic subunit of protein kinase A in cortisol-secreting adenomas (Beuschlein et al. 2014; Lodish and Stratakis 2016).

Loss of heterozygosity or inactivating mutations have been detected in *ARMC5* (Armado-like repeat-containing protein 5) in more than half of cortisol-secreting adenomas resected from patients with bilateral macronodular adrenal hyperplasia. In such patients, there was one germline and one somatic mutation, establishing *ARMC5* as a tumor suppressor gene (Assie et al. 2013). Similarly, adrenocortical lesions including diffuse hyperplasia, nodular hyperplasia, adenoma, and rarely carcinoma may occur as part of the multiple endocrine neoplasia type 1 syndrome, an autosomal dominant disorder, in which there is homozygous inactivation of the *menin* (*MEN1*) tumor suppressor gene on chromosome 11q13.

Finally, some cases of Carney complex have been mapped to chromosome 2p16 but the involved gene has not been identified.

**Clinical manifestations.** The disorder appears to be more severe and the clinical findings more flagrant in infants than in older children. The face is rounded, with prominent cheeks and a flushed appearance (moon faces). Generalized obesity is common in younger children. Hypertension is common (occurring in approximately half of affected children) (Cicala and Mantero 2010) and may occasionally lead to heart failure. In children with adrenal tumors, signs of abnormal masculinization occur frequently; accordingly, there may be hirsutism on the face and trunk, pubic hair, acne, deepening of the voice, and enlargement of the clitoris in girls. Growth is impaired, with length falling below the third percentile, except when significant virilization produces normal or even accelerated growth.

In older children, in addition to obesity, short stature is a common presenting feature. Gradual onset of obesity and deceleration or cessation of growth may be the only early manifestations. Older children most often have more severe obesity of the face and trunk compared with the extremities. Purplish striae on the hips, abdomen, and thighs are common. Hypertension and hyperglycemia usually occur; hyperglycemia may progress to frank diabetes. Pubertal development may be delayed, or amenorrhea may occur in girls past menarche. Weakness, headache, and emotional lability may be prominent. Osteoporosis is common and may cause pathologic fractures.

**Laboratory findings.** Cortisol levels in blood are normally elevated at 8 a.m. and decrease to less than 50% by midnight except in infants and young children in whom a diurnal rhythm is not always established. In patients with Cushing's syndrome, this circadian rhythm is lost; midnight cortisol levels  $>4.4$  mcg/dl strongly suggest the diagnosis. It is difficult to obtain diurnal blood samples as part of an outpatient evaluation, but cortisol can be measured in saliva samples, which can be obtained at home at the appropriate times of day. Elevated nighttime salivary cortisol levels raise suspicion for Cushing's syndrome (Arnaldi et al. 2003; Batista et al. 2007).

Excretion of free cortisol is increased. This is best measured in a 24-h urine sample and is expressed as a ratio of micrograms of cortisol

excreted per gram of creatinine. This ratio is independent of body size and completeness of the urine collection.

A single-dose dexamethasone suppression test is often helpful; a dose of 25  $\mu\text{g}/\text{kg}$  (maximum of 2 mg) given at 11 p.m. results in a plasma cortisol level of less than 5  $\mu\text{g}/\text{dL}$  at 8 a.m. the next morning in normal individuals but not in patients with Cushing's syndrome. It is prudent to measure the dexamethasone level in the same blood sample to ensure adequacy of dosing (Arnaldi et al. 2003; Batista et al. 2007).

A glucose tolerance test is often abnormal. Levels of serum electrolytes are usually normal, but potassium may be decreased, especially in patients with tumors that secrete ACTH ectopically.

After the diagnosis of Cushing's syndrome has been established, it is necessary to determine whether it is caused by a pituitary adenoma, an ectopic ACTH-secreting tumor, or a cortisol-secreting adrenal tumor. ACTH concentrations are usually suppressed in patients with cortisol-secreting tumors and are very high in patients with ectopic ACTH-secreting tumors, but may be normal in patients with ACTH-secreting pituitary adenomas. After an intravenous bolus of corticotropin-releasing hormone (CRH), patients with ACTH-dependent Cushing's syndrome have an exaggerated ACTH and cortisol response, whereas those with adrenal tumors show no increase in ACTH and cortisol. The two-step dexamethasone suppression test consists of administration of dexamethasone, 30 and 120  $\mu\text{g}/\text{kg}/24$  h in four divided doses, on consecutive days. In children with pituitary Cushing's syndrome, the larger dose, but not the smaller dose, suppresses serum levels of cortisol. Typically, patients with ACTH-independent Cushing's syndrome do not show suppressed cortisol levels with dexamethasone.

CT detects virtually all adrenal tumors larger than 1.5 cm in diameter. MRI may detect ACTH-secreting pituitary adenomas, but many are too small to be seen; the addition of gadolinium contrast increases the sensitivity of detection. Bilateral inferior petrosal blood sampling to measure concentrations of ACTH before and after CRH

administration may be required to localize the tumor when a pituitary adenoma is not visualized; this is not routinely available in many centers.

**Differential diagnosis.** Cushing's syndrome is frequently suspected in children with obesity, particularly when striae and hypertension are present. Children with simple obesity are usually tall, whereas those with Cushing's syndrome are short or have a decelerating growth rate. Although urinary excretion of cortisol is often elevated in simple obesity, salivary nighttime levels of cortisol are normal and cortisol secretion is suppressed by oral administration of low doses of dexamethasone.

Elevated levels of cortisol and ACTH without clinical evidence of Cushing's syndrome occur in patients with generalized glucocorticoid resistance (Charmandari et al. 2008). Affected patients may be asymptomatic or exhibit hypertension, hypokalemia, and precocious pseudopuberty; these manifestations are caused by increased mineralocorticoid and adrenal androgen secretion in response to elevated ACTH levels. Mutations in the glucocorticoid receptor have been identified.

**Treatment.** Transsphenoidal pituitary microsurgery is the treatment of choice in pituitary Cushing's disease in children (Barker et al. 2003; Wilson 2012). The overall success rate with follow-up of less than 10 years is 60–80%. Low postoperative serum or urinary cortisol concentrations predict long-term remission in the majority of cases. Relapses are treated with reoperation or pituitary irradiation.

Cyproheptadine, a centrally acting serotonin antagonist that blocks ACTH release, has been used to treat Cushing's disease in adults; remissions are usually not sustained after discontinuation of therapy. Experience with this agent is limited in children, given that surgical cure is attempted whenever possible. Inhibitors of adrenal steroidogenesis (metyrapone, ketoconazole, aminoglutethimide, etomidate) have been used preoperatively to normalize circulating cortisol levels and reduce perioperative morbidity and mortality. Pasireotide, a somatostatin antagonist with high affinity for the somatostatin receptor type 5 (the main subtype on corticotrophs), is effective in lowering cortisol levels in ~25% of

patients with unresected Cushing's disease (Colao et al. 2012; Lacroix et al. 2015). If a pituitary adenoma does not respond to treatment, or if ACTH is secreted by an ectopic metastatic tumor, the adrenal glands may need to be removed. This can often be accomplished laparoscopically. Adrenalectomy may lead to increased ACTH secretion by an unresected pituitary adenoma, evidenced mainly by marked hyperpigmentation; this condition is termed Nelson syndrome.

Management of patients undergoing adrenalectomy requires adequate preoperative and postoperative replacement therapy with a corticosteroid. Tumors that produce corticosteroids usually lead to atrophy of the normal adrenal tissue, and replacement with cortisol (10 mg/M<sup>2</sup>/24 h in three divided doses after the immediate postoperative period) is required until there is recovery of the hypothalamic-pituitary-adrenal axis, which takes an average of 12 months (Lodish et al. 2012).

## Generalized Glucocorticoid Resistance

**Pathophysiology.** Patients with generalized glucocorticoid resistance have target-tissue insensitivity to glucocorticoids (Charmandari et al. 2013). The condition is usually inherited in an autosomal dominant manner but sporadic cases occur. Impairment of normal negative feedback of cortisol at the levels of the hypothalamus and pituitary activates the HPA axis with consequent increases in ACTH and cortisol concentrations. Generalized glucocorticoid resistance is caused by (usually heterozygous) inactivating mutations in the glucocorticoid receptor, encoded by the NR3C1 gene.

**Clinical manifestations.** The excess ACTH secretion causes adrenal hyperplasia with increased production of adrenal steroids. Cortisol concentrations are elevated but do not cause Cushing's syndrome because of the insensitivity to glucocorticoids; conversely, most signs and symptoms of adrenal insufficiency are absent except for the frequent occurrence of chronic fatigue and occasional anxiety. On the other



hand, the mineralocorticoid and androgen receptors are normally sensitive to their ligands. Signs of mineralocorticoid excess, such as hypertension and hypokalemic alkalosis, are frequently noted owing to elevated levels of deoxycorticosterone. Increased concentrations of adrenal androgens may cause ambiguous genitalia in girls and gonadotropin-independent precocious puberty in children of either gender, acne, hirsutism and infertility in both sexes, menstrual irregularities in females, and oligospermia in males. Testicular adrenal rest tumors and ACTH-secreting pituitary adenomas occasionally occur.

**Laboratory findings.** The diagnosis of generalized glucocorticoid resistance is suggested by elevated serum cortisol concentrations and increased 24-h urinary-free cortisol excretion in the absence of Cushing's syndrome. Levels of other adrenal steroids are also increased. Plasma concentrations of ACTH may be normal or high. The circadian pattern of ACTH and cortisol secretion is preserved, although at higher than normal concentrations, and there is resistance of the HPA axis to dexamethasone suppression. Sequencing of the NR3C1 gene can confirm the diagnosis, but is not routinely available.

**Differential diagnosis.** Generalized glucocorticoid resistance can be distinguished from relatively mild cases of Cushing's syndrome by excessive weight gain and poor linear growth in patients with the latter condition. Adrenocortical tumors may secrete mineralocorticoids such as deoxycorticosterone and also androgens, but ACTH levels are often suppressed, and of course the tumor can usually be visualized with CT or MRI. Congenital adrenal hyperplasia owing to 11 $\beta$ -hydroxylase deficiency may present with hypertension and signs of androgen excess, but cortisol levels are low, and levels of cortisol precursors (17-hydroxyprogesterone, 11-deoxycortisol) are elevated. Obese patients may be hypertensive and have hyperandrogenism, but cortisol secretion should be readily suppressed by dexamethasone.

**Treatment.** The goal of treatment is to suppress the excess secretion of ACTH, thereby suppressing the increased production of adrenal steroids with mineralocorticoid and androgenic

activity. This requires administration of high doses of a pure glucocorticoid agonist such as dexamethasone (typically ~20–40  $\mu\text{g}/\text{kg}/\text{day}$ ) with careful titration to suppress endogenous corticosteroid secretion without causing signs of glucocorticoid excess such as excessive weight gain or suppression of linear growth.

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## Hyperthyroidism

### Pathophysiology

*Synthesis, regulation, and actions of thyroid hormones.* Thyroid hormones are synthesized in follicular cells. Adjacent tyrosine residues on thyroglobulin (which has around 120 tyrosines) are iodinated by thyroid peroxidase; the adjacent phenolic rings are conjugated and the hormones released by proteolysis. There are two active hormones, thyroxine (T4) and triiodothyronine (T3); the latter is approximately four times as active as, but has a much shorter half-life than, thyroxine. Both are synthesized de novo; additionally, type 1 and particularly type 2 deiodinases convert T4 to T3 (Dumitrescu and Refetoff 2007).

Synthesis is regulated at the hypothalamic and pituitary levels by thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH), respectively. Thus TSH levels are high in patients with primary hypothyroidism and suppressed in patients with hyperthyroidism. TSH signals via a G protein-coupled receptor on the surface of follicular cells to increase thyroid hormone synthesis (Gershengorn and Neumann 2012; Kleinau and Krause 2009).

Thyroid hormones act via thyroid hormone receptors that are members of the nuclear hormone receptor superfamily. There are two distinct genes, THRA and THRB, encoding receptors that are expressed in different tissues; each can bind DNA as monomers, as homodimers, or as heterodimers with the retinoid X receptor (RXR). Thyroid hormones have important permissive effects on neural development, skeletal maturation, and somatic growth, and they increase rates of cellular metabolism (Brenta et al. 2007). Most importantly in the context of this chapter, they regulate

sensitivity to catecholamines in both the cardiovascular and nervous systems (Silva and Bianco 2008). Thus, hyperthyroidism (if symptomatic, termed thyrotoxicosis) causes signs and symptoms very similar to those of catecholamine excess as might be seen in pheochromocytoma.

**Thyrotoxicosis.** Two autoimmune diseases can cause thyrotoxicosis. Graves' disease is caused by antibodies to the thyroid-stimulating hormone (TSH) receptor that interact with the receptor to activate it in the same way that would occur by occupation by its physiologic ligand (TSH). These are termed thyroid-stimulating antibodies (TSI). Chronic lymphocytic (Hashimoto's) thyroiditis is more often associated with hypothyroidism, but it can present with a thyrotoxic phase, in which autoimmune destruction of thyroid cells by cytotoxic lymphocytes causes them to release their contents of thyroxine (T4) and triiodothyronine (T3). Finally, hyperfunctioning ("hot") thyroid nodules can cause thyrotoxicosis; these are rare in children.

**Clinical manifestations.** Patients have typically lost weight. They have tachycardia and hypertension (mainly systolic) with wide pulse pressure. Hyperpyrexia is present only in very severe cases ("thyroid storm") and is an indication for hospitalization to stabilize the patient. Thyroid enlargement is highly variable and need not be present. The gland may have a firm or micronodular consistency; a single palpable nodule should raise suspicion for a hyperfunctioning nodule and prompt a thyroid scan (see below). There is often a bruit or thrill over the thyroid. The precordium is hyperdynamic. Patients appear nervous and often give a history of poor school performance with inability to pay attention in class. They are usually tremulous, with tremors most easily elicited by having the patient extend the hands or the tongue, and they have brisk reflexes, often with a mild to moderate degree of clonus.

A lid lag can often be elicited by having the patient look rapidly downward (the lids do not immediately drop as they would normally do). Other ocular findings are pathognomonic for Graves' disease, including conjunctival injection, puffy eyelids, and proptosis.

**Laboratory findings.** TSH levels are usually undetectably low. Total and free T4 levels are elevated. Total T3 levels are also elevated, and because T3 has a much shorter half-life than T4, it is particularly useful for monitoring the short-term response to treatment. Levels of antibodies to thyroid proteins – antithyroid peroxidase and anti-thyroglobulin – are usually elevated in both Graves' disease and Hashimoto's thyroiditis, but thyroid-stimulating antibodies are elevated only in Graves' disease and are useful for distinguishing the two conditions. Radioactive iodine (I-123) uptake is increased in Graves' disease but decreased in Hashimoto's thyroiditis, even in the thyrotoxic phase. A thyroid scan after I-123 administration may detect a hot nodule.

**Treatment.** The hypertension, tachycardia, and tremulousness may all be treated by beta-blockade, typically with 25–50 mg per day of atenolol. This is continued until thyroid hormone levels have returned to normal with specific treatment. There are three long-term treatments for thyrotoxicosis (Bahn et al. 2011). Thionamide drugs can suppress thyroid hormone synthesis and are useful for both Graves' disease and the thyrotoxic phase of Hashimoto's thyroiditis. In the United States, methimazole is the main agent used (initially ~0.5 mg/kg/d in two divided doses); propylthiouracil was extensively used in the past but is no longer recommended, particularly in children, because of the risk of liver failure (Rivkees and Mattison 2009). Methimazole frequently causes rashes or other allergic reactions and may cause agranulocytosis or liver failure; thus complete blood counts and transaminases should be monitored. The dose of medication can usually be decreased after the patient is euthyroid. Approximately 20% of patients with Graves' disease eventually remit and can be completely weaned off medication. Patients with Hashimoto's thyroiditis typically "burn out" after a few months and must be weaned off methimazole; they usually also require thyroid replacement with levothyroxine.

Two other approaches are relevant mainly to Graves' disease; their relative merits are somewhat controversial. Radioactive iodine (I-131) is

specifically taken up by the thyroid gland and can ablate thyroid cells with relatively limited whole-body radiation exposure. Rarely used in children 20 years ago, it is becoming increasingly accepted in teenagers and older schoolchildren, even as initial treatment (Rivkees and Dinauer 2007). Risks of causing a thyroid adenoma may be minimized by aiming to completely ablate thyroid function rather than trying to render the patient euthyroid. Nevertheless, the author believes that a risk of subsequent thyroid tumors may exist before 8 years of age (based on data from atomic bombs and Chernobyl) and that it is more prudent in a young child to temporize with methimazole until the patient is older, as long as the drug is well tolerated. Alternatively, the thyroid may be removed surgically (Lee et al. 2007). This has a low risk of long-term complications but requires an experienced surgeon to avoid hypoparathyroidism or damage to the recurrent laryngeal nerve. Hemithyroidectomy is the treatment of choice for a hyperfunctioning nodule.

## Conclusion

Endocrine disorders such as pheochromocytoma, congenital adrenal hyperplasia, Cushing's syndrome, primary aldosteronism, and hyperthyroidism collectively account for a small proportion of cases of hypertension in children, but the hypertension is often relatively severe. It is important to accurately diagnose these disorders because the associated hypertension usually requires, and responds well to, specific treatment of the underlying condition.

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## Abstract

Neonatal hypertension as a clinical entity has been recognized since the 1970s, and yet we still do not have a complete understanding of the physiologic blood pressure changes occurring over the first year of life. Blood pressure changes rapidly in the newborn period during hemodynamic adaptation to the extrauterine environment, especially in preterm neonates. Measurement methods have evolved to less-invasive blood pressure monitoring, but there are still improvements needed in measurement techniques. The incidence of neonatal hypertension does not seem to be increasing despite increasing complexity of the population due to technologic advances. Risk factors or causes of hypertension can be found in most infants but treatment can be challenging. Most infant hypertension resolves over time although premature and low birth weight infants are at risk of future hypertension. This chapter will describe proper measurement of infant blood pressure, illustrate the expected changes in blood pressure during the first year of life, as well as explore evaluation, management, and follow-up of neonatal and infant hypertension.

## Keywords

Neonatal blood pressure • Neonatal hypertension • Infant hypertension • Blood pressure measurement • Hypertension risk factors • Hypertension management

## Abbreviations

ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin-converting enzyme
ECMO	Extracorporeal membrane oxygenation
IV	Intravenous
MAP	Mean arterial pressure
NICU	Neonatal intensive care unit
PDA	Patent ductus arteriosus
RAAS	Renin-angiotensin-aldosterone system
RVT	Renal vein thrombosis
SGA	Small for gestational age
UAC	Umbilical artery catheter
VLBW	Very low birth weight

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## Introduction

The incidence of hypertension in the neonatal intensive care unit (NICU) is around 1–2%. It is much less common than is neonatal hypotension, and therefore clinicians in the NICU may be less comfortable with the proper assessment and management of elevated blood pressures. In fact, around one quarter of neonates diagnosed with hypertension in the NICU are not treated with antihypertensive medications. Fortunately, various risk factors or causes of hypertension are able to be determined in most every patient. Recent studies are suggesting that hypertension in preterm infants may be different than hypertension in term infants in etiology and response to treatment. When the hypertension is related to perinatal events, the majority of neonates and infants will have normalization of their blood pressure over the first years of life. Proper management of these infants is important as there is more and more evidence that future cardiovascular health can be affected by perinatal conditions.

## Measurement of Blood Pressure

The gold standard blood pressure measurement technique in neonates is direct intra-arterial monitoring. Common sites for catheterization in neonates are the umbilical and radial arteries, which have demonstrated comparable blood pressure values in this population. Direct intra-arterial monitoring may be necessary in the most acutely ill neonates although there has been a shift to noninvasive blood pressure monitoring for the majority of the neonates within an NICU. Indirect methods for measuring blood pressure include ultrasonic Doppler and oscillometric methods. Palpation and auscultation using a sphygmomanometer are not practical within the NICU setting but may be used in older infants in a clinic setting.

Ultrasonic Doppler assessment involves inflation then deflation of a sphygmomanometer with detection of blood flow or motion of the vessel wall with a Doppler device. With experienced users, the systolic blood pressure can easily be detected, but diastolic blood pressure is often unmeasurable. The technique that has become more common within the NICU and follow-up clinics is the oscillometric method. A blood pressure cuff inflates above systolic blood pressure, and then as it deflates, the oscillometric device detects the maximum pressure oscillations within the artery determining the mean arterial pressure (MAP). The machine then uses an algorithm specific to each device to calculate systolic and diastolic blood pressure. Therefore, the MAP is the most accurate pressure reading with systolic and diastolic values less precise. When oscillometric blood pressures were compared to radial arterial blood pressures in infants and children, there was good correlation between the two methods, and the oscillometric readings were better than values determined by auscultation (Park and Menard 1987). Even in premature infants, these noninvasive blood pressures correlate well with intra-arterial monitoring (Meyer et al. 2010).

As each oscillometric monitor uses independent algorithms for determination of blood pressure values, several studies have compared multiple devices for accuracy. Dannevig et al. (2005) compared three monitors: Dinamap



Compact™, Hewlett-Packard™, and Criticare™ models. When compared to intra-arterial blood pressures, they found that the Hewlett-Packard™ model had lower values than invasive monitoring, while the Dinamap™ and Criticare™ tended to read higher and that the deviance was dependent on the size of the infant. The Hewlett-Packard™ showed lower values in the larger infants, while the Criticare™ and Dinamap™ values were too high in the smallest infants which could lead to under-recognition of hypotension. Another study comparing three oscillometric devices to intra-arterial monitoring found that all three devices overestimated mean blood pressure by 3–8 mmHg (O’Shea and Dempsey 2009). Clinicians who use the oscillometric machines should be aware of the limitations of the specific device that they choose to use in order to avoid misinterpretation of blood pressure values.

The potential for under-recognition of hypotensive events is worrisome, especially in critically ill premature neonates. Takci et al. (2012) showed good correlation of invasive and noninvasive mean blood pressures except when the MAP was less than or equal to 30 mmHg where the oscillometric device readings were too high. Lalan and Blowey (2014) found oscillometry overestimated blood pressures compared to radial intra-arterial monitoring by 4–8 mmHg. While the mean MAP was similar for oscillometric measures and umbilical artery catheter (UAC) readings, the standard deviation was high at almost 10 mmHg, and therefore the authors continue to recommend intra-arterial monitoring for sick neonates.

Other less common methods of blood pressure measurement have been used by practitioners experienced in the techniques. A recent study compared blood pressure values by oscillometry, flush method, and pulse oximetry to Doppler ultrasound and found the best correlation with flush method and pulse oximetry (Ribeiro et al. 2011). Another area of debate within some NICU settings is around the use of calf blood pressure measurements. Systolic blood pressure by calf measurements is slightly lower but similar to arm measurements until about 6 months of age when the calf pressures begin to exceed arm blood pressures (Crapanzano et al. 1996). Unfortunately, the calf blood pressure

values show more variability than arm blood pressures and therefore should only be used in exceptional circumstances when arm blood pressure values are not feasible prior to 6 months of age and then not used after 6 months of age.

The state of the infant at the time the blood pressure is being measured is important and can influence the blood pressure value. Early observations of blood pressures in neonates showed that the blood pressure was lower when the neonate was in deep sleep and rose above baseline when crying, being held head up, and during feeding (Gupta and Scopes 1965). The elevation of blood pressure with feeding is up to 20 mmHg higher. This observation has been confirmed in neonates within the first days of life having blood pressures increasing significantly during feeding, and the magnitude of elevation may be influenced by the volume of fluid intake within the first few minutes of feeding (Cohen et al. 1998). In follow-up clinics of infants and young children, the non-calm state has been associated with blood pressures 17–30 mmHg higher than when the infant is calm (Duncan et al. 2008). It is therefore sometimes necessary to attempt blood pressures on several occasions or in different settings in order to achieve an accurate calm measurement.

Accurate blood pressure measurement is important in neonates and infants, especially when the blood pressure factors into clinical decision-making. Some authors suggest that the median of three oscillometric blood pressure measurements should be used (Thoesen and Cowan 1992), while others state that one blood pressure during routine vitals is adequate, in calm healthy term newborns (Sarici et al. 2000). The cuff size is critically important to accurate blood pressure measurement, and the cuff width/arm circumference ratio should be between 0.45 and 0.70 (Kimble et al. 1981). As well, attention to the MAP as the most accurate measure of blood pressure is essential as this is the parameter actually measured by oscillometric devices. While physicians in critical care medicine are used to evaluating mean pressures, most pediatric nephrologists are more comfortable with systolic and diastolic blood pressures due to the use of auscultatory methods in most older children.

**Table 1** Protocol for blood pressure measurement in neonates using an oscillometric device

Prone or supine position
Use right upper arm
Cuff width/arm circumference ratio between 0.45 and 0.70
Apply cuff and leave infant undisturbed for 15 min
Take readings when infant is asleep or in quite-awake state
Three blood pressure readings at 2 min intervals
1.5 h after feed or medical intervention where possible

Adapted from Nwankwo et al. (1997)

Adapting to the use of MAP within the NICU would be more useful.

The use of a standard protocol for newborn blood pressure measurement has been suggested by Nwankwo et al. (1997) (see Table 1). They found in infants weighing less than 2,500 g, when compared to routine nursing care, standardized blood pressures were significantly lower and showed less variability. First blood pressure readings were significantly higher than third readings lending support to the need for multiple measurements. Other than waiting for one and a half hours after a feed or medical intervention to take a blood pressure, the protocol is reasonable for use within the NICU setting, especially when clinical decisions are being based on the blood pressure values.

## Factors Influencing Blood Pressure

Various factors, both extrinsic (maternal) and intrinsic (infant), can influence newborn blood pressure values. Maternal blood pressure and/or hypertension have been related to higher newborn blood pressures in several studies (Gillman et al. 2004; Seliem et al. 2007). Maternal age has been positively correlated with newborn blood pressure in one study (Gillman et al. 2004) but not consistently in other studies (Sedaghat et al. 2008; Sadoh and Ibhanebhor 2010). Maternal diabetes may be related to higher newborn blood pressure especially when birth is earlier in gestation (Kent et al. 2009b). Studies on the effect of maternal smoking on infant and childhood blood pressure have been conflicting. A birth cohort study demonstrated male infants of maternal smokers had

blood pressures more than 8 mmHg higher than non-smokers, although the increase was not seen in female offspring (Geerts et al. 2007). The prenatal exposure to “secondhand smoke” seems to lead to alterations in infant circulatory control mechanisms (Cohen et al. 2010). A recent study has also correlated prenatal exposure to air pollution with newborn blood pressure (van Rossem et al. 2015). Maternal body mass index >30 and low socioeconomic status were associated with higher newborn systolic blood pressure in a Nigerian study, although birth weight was still the strongest predictor (Sadoh and Ibhanebhor 2010). Likely, even maternal nutritional intake has an effect on infant blood pressure, with a u-shaped curve for infant blood pressure and maternal carbohydrate intake (Aaltonen et al. 2008). Maternal protein intake does not seem to have the same effect in infancy (Huh et al. 2005).

Perinatal events may also influence newborn blood pressures. Antenatal steroids given within 7 days of birth can reduce respiratory distress syndrome, but the effect on newborn blood pressure has been controversial. Some studies found higher newborn blood pressures (Seliem et al. 2007; Been et al. 2009; Vesoulis et al. 2016), while others did not (Dagle et al. 2011; LeFlore et al. 2000). A recent randomized double-blind, placebo-controlled trial showed no difference in newborn blood pressures in infants that were exposed to repeated doses of prenatal corticosteroids compared to single dose (Mildenhall et al. 2009). As antenatal steroids may have an effect on function of the infant hypothalamic-pituitary-adrenal axis, the way in which the placenta handles the steroids seems to also play a role in how steroids can influence infant blood pressure (Stark et al. 2009). Maternal hemolysis, elevated liver enzymes, and low platelets or HELLP syndrome and chorioamnionitis have been associated with lower blood pressures in neonates (Been et al. 2009; Vesoulis et al. 2016). Maternal hypertension management with labetalol may be related to neonatal hypotension, while the use of other antihypertensives or magnesium sulfate does not seem to have an effect (Heida et al. 2012). Even the mode of delivery and type of maternal anesthetic may have an impact on newborn blood pressures, with elective cesarean

section and spinal anesthesia being related to lower systolic blood pressures in newborns (Sedaghat et al. 2008; Satoh et al. 2016).

The most strongly correlated intrinsic or infant factors associated with newborn blood pressure are birth weight and gestational age. The earlier in gestation that the neonate is born, the lower the expected initial blood pressure values with essentially a linear relationship (Zubrow et al. 1995; Pejovic et al. 2007). This same relationship has been shown for birth weight and blood pressure. Being born small for gestational age (SGA) may also be associated with lower initial blood pressure values (Lurbe et al. 2007). Congenital renal, cardiac, or endocrine anomalies may influence blood pressure and are associated with a higher prevalence of neonatal hypertension. The influence of fluid volume and vasoactive regulators on neonatal blood pressure is demonstrated in infant pairs of twin-twin transfusion syndrome where blood pressures in recipients are significantly higher than donors (Mercanti et al. 2011). In fact, 14% of twin-twin transfusion recipients are hypertensive. And while it is common to find low blood pressure in neonates with blood stream infections, a recent study has shown that blood pressures actually increase in the days just prior to the clinical sepsis (Yapiciglu et al. 2015).

Not surprisingly, genetics also likely plays a role in which infants develop hypertension. Cytochrome P450 CYP2D6 “CC” genotype was associated with increased risk of elevated blood pressure in infants born less than 32 weeks of gestation during neonatal and follow-up periods (Dagle et al. 2011). All these various factors, including antenatal and postnatal exposures, gestational age, clinical condition, and genetic predisposition, probably interact in complex ways to influence neonatal blood pressures.

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## Normative Data

### Day 1 of Life

Newborn blood pressure on the first day of life is strongly positively correlated with both birth weight and gestational age. The Philadelphia

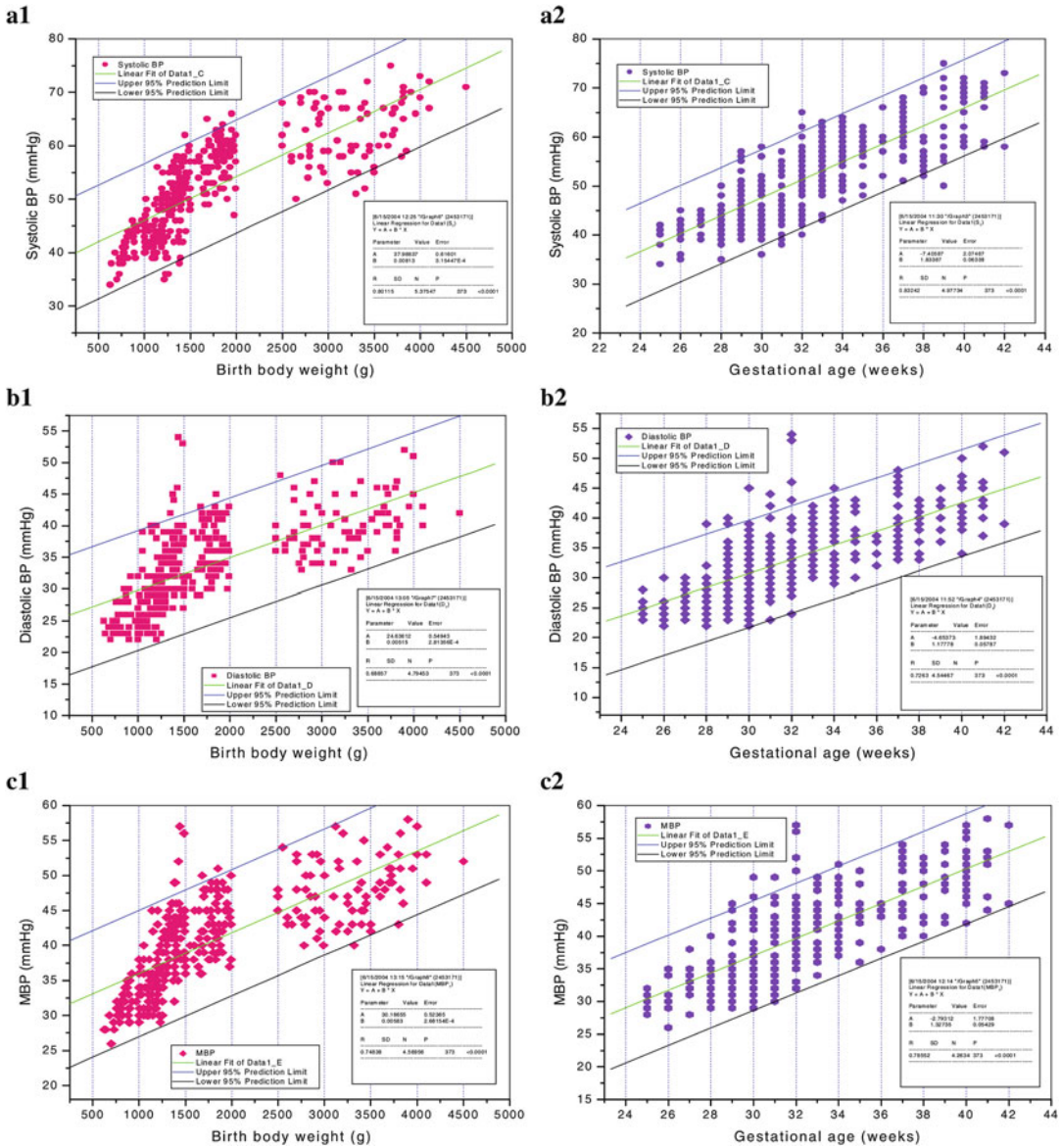
Neonatal Blood Pressure Study Group clearly demonstrated this correlation when they studied all infants admitted to 14 level III NICUs and analyzed blood pressure values of over 300 infants on day 1 of life (Zubrow et al. 1995). Their blood pressure nomograms have been the most widely used reference values. Similar to the blood pressure standards used in older children, the preference should be to use reference values determined from stable neonates as a better predictor of what is expected in healthy newborns. A more recent study of almost 400 hemodynamically stable infants has shown a similar correlation of gestational age and birth weight with blood pressure in neonates on day 1 of life, presented with 95% upper and lower confidence limits for ease of use (Pejovic et al. 2007) (see Fig. 1).

### First Days of Life

In very low birth weight (VLBW) infants, systolic, diastolic, and mean blood pressures increase by more than 30% over the first few days of life which illustrates the significant physiologic changes that occur as neonates adapt to the extra-uterine environment (Leflore et al. 2000). The mechanisms responsible for these dramatic changes are still being determined, but likely involve loss of vasodilator substances important during the in utero environment and maturation of factors controlling vascular tone (LeFlore et al. 2000; Joppich et al. 1979). The Philadelphia study showed that all infants in the NICU, regardless of gestational age, have a rapid increase in blood pressure over the first 5 days of life with increments around 1.5–2.5 mmHg/day (Zubrow et al. 1995). This differs from healthy term infants on the postnatal ward where blood pressure values are higher on day 2 compared to day 1 of life but not consistently thereafter (Kent et al. 2007a).

### First Weeks of Life

In the first weeks of life, the rate of blood pressure change and the length of time over which the blood pressure is rapidly increasing may differ

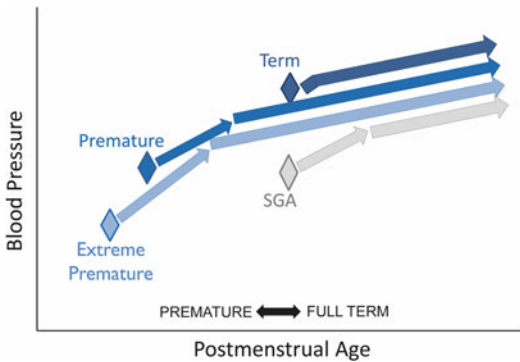


**Fig. 1** Neonatal blood pressure on day 1 of life is positively correlated with birth weight (1) and gestational age (2). Systolic (a), diastolic (b), and mean (c) blood pressures are presented with 95 % confidence limits (Pediatric

Nephrology, Blood pressure in non-critically ill preterm and full-term neonates, volume 22, 2007, pages 249–257, Pejovic B, Peco-Antic A, Marinkovic-Eric J, with permission of Springer)

based on gestational age at birth or birth weight. The study by Pejovic et al. (2007) found that the neonates with the lowest gestational age at birth had the most rapid rate of rise of blood pressure. In infants born at less than 28 weeks gestational age, the average increase in mean blood pressure was 26% in the first week and 51% in the first month

compared to 13% and 22% in full-term infants. Another study of stable premature infants showed that the infants born at 28–31 weeks gestational age had a significant increase in blood pressure over the first 2–3 weeks of life, while the infants born at 32–36 weeks had a rapid increase over only 1 week (Kent et al. 2009a). The authors



**Fig. 2** Illustration of patterns of neonatal blood pressure changes when born at term or premature, extremely premature, or small for gestational age (SGA)

suggested that the blood pressure values at the end of the rapid increase were similar to term infants in the first days of life.

In the longer term, Georgieff et al. (1996) determined VLBW infants had similar blood pressure values to other NICU graduates at 4 months corrected age despite remaining smaller in length and weight. As blood pressures were not measured between discharge and 4 months of age, we do not know when the catch-up occurred. A study of full-term newborns found that the infants with the lowest birth weights, particularly the SGA infants, had the lowest blood pressures initially but then had the most rapid rate of rise of blood pressure (Lurbe et al. 2007). By 1 month of age, all term infants had similar blood pressures that remained comparable throughout the first year of life. The multitude of variations in blood pressure patterns over the first weeks of life is represented in Fig. 2.

Infant blood pressures have also been described as increasing with weight and with postmenstrual age. Lalan and Blowey (2014) recently derived a graph of intra-arterial MAP by postnatal weight with a slope showing that the MAP increased by 35 mmHg for every kilogram in weight gained. Zubrow et al. (1995) developed a clinically useful graphical reference of blood pressure increase by postconceptional age for neonates after the first day of life. Recognizing that infant blood pressures over the first 2 weeks are rapidly changing and could influence nomograms

by postmenstrual age, Dionne et al. (2012) derived normative values for blood pressures after 2 weeks of life based on current postmenstrual age from the available published literature (see Table 2). Fiftieth, 95th, and 99th percentiles were calculated as a reference for clinicians.

### First Year of Life

The blood pressure changes over the first year of life are less marked than in the newborn period. Blood pressure values increase steadily until 3–6 months of age at which time the values remain stable up to 1 year of age. The most widely used nomograms for infant blood pressure come from the Report of the Second Task Force on Blood Pressure from the National Heart, Lung, and Blood Institute (1987) (see Fig. 3). The infant blood pressures were measured using the Doppler method, which likely provides slightly lower readings than by the oscillometric method commonly used today. A more recent study of over 400 healthy term infants whose blood pressures were measured by oscillometric method shows a similar trend in blood pressure over the first year of life (Kent et al. 2007b). The blood pressures were only measured on day 2 of life and at 6 and 12 months of age and therefore do not provide normative data for ages in between. Large-scale studies of oscillometric blood pressure values over the first year of life are desperately needed.

### Definition of Hypertension

Various definitions of infant hypertension have been used since high blood pressure was recognized as an issue in neonates and infants. This has made the comparison of studies and the determination of the incidence of hypertension challenging. Earlier studies used set blood pressure values for all term or preterm infants. As studies were published of normative values with percentiles, then clinicians applied the concept used in older children and adopted the 95th percentile blood pressure as the definition of hypertension.

**Table 2** Infant blood pressures by postmenstrual age after 2 weeks of life; systolic blood pressure (SBP), mean arterial pressure (MAP), and diastolic blood pressure (DBP) are presented as 50th, 95th, and 99th percentiles

Postmenstrual age	Blood pressure	50th percentile	95th percentile	99th percentile
44 weeks	SBP	88	105	110
	MAP	63	80	85
	DBP	50	68	73
42 weeks	SBP	85	98	102
	MAP	62	76	81
	DBP	50	65	70
40 weeks	SBP	80	95	100
	MAP	60	75	80
	DBP	50	65	70
38 weeks	SBP	77	92	97
	MAP	59	74	79
	DBP	50	65	70
36 weeks	SBP	72	87	92
	MAP	57	72	77
	DBP	50	65	70
34 weeks	SBP	70	85	90
	MAP	50	65	70
	DBP	40	55	60
32 weeks	SBP	68	83	88
	MAP	49	64	69
	DBP	40	55	60
30 weeks	SBP	65	80	85
	MAP	48	63	68
	DBP	40	55	60
28 weeks	SBP	60	75	80
	MAP	45	58	63
	DBP	38	50	54
26 weeks	SBP	55	72	77
	MAP	38	57	63
	DBP	30	50	56

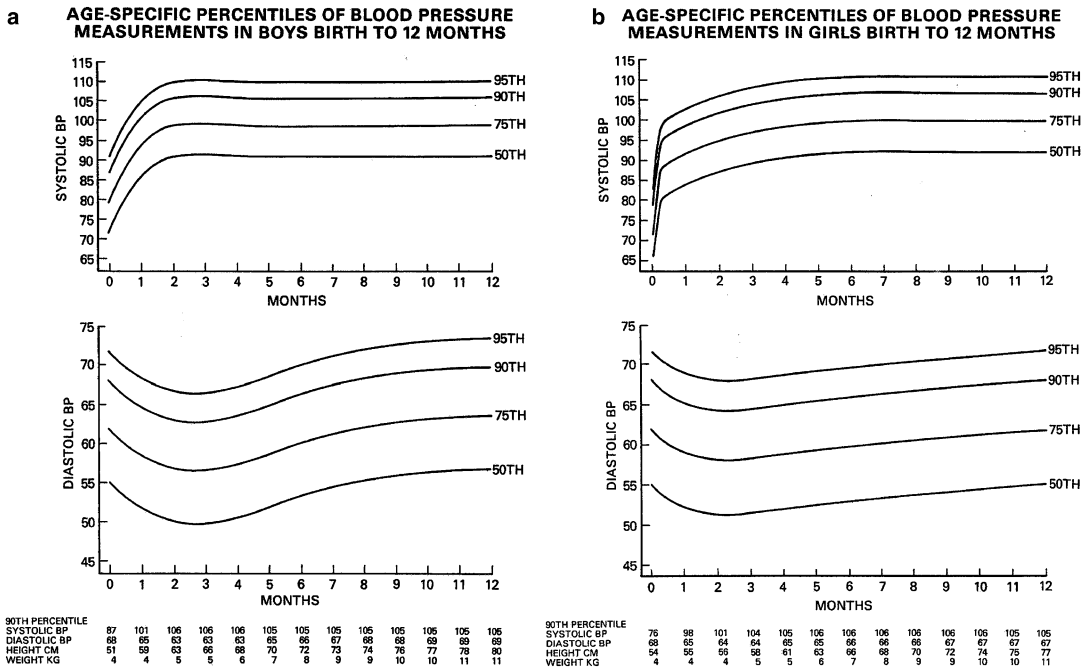
Adapted from Dionne et al. (2012)

Unfortunately, we do not have outcome studies in infants to support or refute the use of this arbitrary definition although in the future this may come from the neurocognitive or cardiovascular literature (Lande et al. 2003; Sharma et al. 2010). In addition, the use of antihypertensive medications in the neonatal and infant population can be associated with risks, and very few studies have been completed in this population. Therefore, at this time the best recommendation for definition of hypertension in neonates would be blood pressure values consistently above the 95th percentile based on postmenstrual age (see Table 2). In older infants, blood pressure values consistently

above the 95th percentile based on curves from the Second Task Force on Blood Pressure (see Fig. 3) should be considered as hypertension and investigated and managed as appropriate.

## Incidence of Hypertension

The incidence of hypertension in general healthy newborns is low, likely around 0.2%, and routine screening of blood pressure is not recommended (Ingelfinger 1982; Committee on Fetus and Newborn 1993). Blood pressures should be checked in infants considered “at risk” which includes NICU



**Fig. 3** Blood pressure percentiles for (a) male infants and (b) female infants from birth to 12 months of age (Reprinted from the Second Task Force on Blood Pressure Control in Children, National Heart, Lung, and Blood Institute (1987))

graduates, infants with congenital heart or kidney disease, or with other conditions known to affect blood pressure (4th Report 2004). In one of the first studies of neonatal hypertension, Adelman (1978) found an incidence of 2.5% in NICU infants when hypertension was defined as a blood pressure >90/60 mmHg in term infants or >80/45 mmHg in preterm infants. A recent large database study of more than 120,000 NICU encounters found an incidence of hypertension of 1.7% in all patients, and 1.0% after infants with congenital cardiac disorders were excluded (Blowey et al. 2011). Similarly, an Australian study of all newborns in a tertiary level NICU found an incidence of neonatal hypertension of 1.3% (Seliem et al. 2007). The median gestational age of these infants was 34 weeks, and the hypertension was diagnosed on average at postnatal day 5 although the range was 2–144 days. This is similar to an earlier study with a mean age of onset of 11 days suggesting that many infants that will develop hypertension do so within the first 1–2 weeks of life (Buchi and Siegler 1986).

It is interesting that the incidence does not seem to be increasing despite the increasing complexity of patients within the NICU. It may be more likely that the incidence of hypertension in this population will be higher during adolescence and adulthood.

### Risk Factors for Hypertension

Various factors have been associated with an increased risk for hypertension in neonates. It is important to recognize that risk factors may not be equivalent to causes as the data may come from sources where a primary cause of the hypertension was not able to be determined, as in a database, or multiple factors may have contributed to the development of hypertension in an individual patient. Also, the risk factor itself may not have been the cause of the hypertension but may be a surrogate for the state or condition of the infant. A recent study found that in preterm infants with hypertension, the etiology was more often related

to perinatal events, while in term infants with hypertension, an underlying cause was more likely to be found (Sahu et al. 2013).

Hypertension is more common in preterm infants and those with lower birth weights with as much as 75% of hypertension occurring in premature infants (Seliem et al. 2007; Sahu et al. 2013). The most commonly reported risk factors include umbilical artery catheters (UAC), chronic lung disease, and patent ductus arteriosus. Other risk factors include renal failure and congenital renal anomalies, intraventricular hemorrhage, steroids, and ECMO (Seliem et al. 2007; Singh et al. 1992; Blowey et al. 2011; Sahu et al. 2013). In a large database study by Blowey et al. (2011), the risk of hypertension was also higher in infants with neonatal asphyxia, seizures, and necrotizing enterocolitis and in those infants with a higher severity of illness score, more coexisting diagnoses, and in those that expired before discharge. Infants with hypertension seem to have a longer length of hospital stay which may be reflective of a more complex and ill population (Blowey et al. 2011; Sahu et al. 2013).

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## Causes of Hypertension

The most common causes of neonatal hypertension are renovascular and renal parenchymal disease, accounting for 25–50% of causes (Singh et al. 1992; Sahu et al. 2013). Cardiovascular causes are essential to diagnose early. The most common respiratory cause is chronic lung disease which may not present with hypertension until several months of age. Endocrine and neoplastic causes of hypertension are less common but important to diagnose as management is specific to each disease. Other causes are often iatrogenic such as pain, medications, and excess salt (see Table 3).

### Renovascular Causes

The association between UACs and renal artery thrombosis has been recognized for decades. The mechanism is likely related to disruption of the vascular endothelium by the catheter with

subsequent development of thrombus and clot extension or release of emboli. The incidence of clot formation associated with umbilical catheters differs widely depending on decade of screening and method of detection. An early study of randomly selected infants found a 95% incidence of clots associated with low thoracic UACs on aortograms (Neal et al. 1972). Seibert et al. (1987) studied neonates with lower placement of UACs and found 26% had an aortic thrombus by ultrasound, of which 29% were asymptomatic, 24% presented with hematuria, and 24% had hypertension. A recent Cochrane review of morbidity associated with UAC placement found high-placed UACs were associated with a lower incidence of clinical ischemic complications, but based on limited studies, it seems that hypertension and hematuria do not differ based on catheter position (Barrington 2010).

Renal artery thrombosis is most commonly associated with the use of UACs, and infants may present with a sudden increase in blood pressure. The incidence of hypertension in infants with a UAC has been reported between 1.6% and 8.8% (Blowey et al. 2011; Singh et al. 1992). In one study, 35% of hypertensive infants with a UAC had associated thrombocytopenia and 25% had lower limb ischemia (Singh et al. 1992). When investigating for this complication, it is important to realize that when clots are found, they are often extending into or originating from the aorta. Sometimes no clots will be found on imaging when the infant is hypertensive, suggesting either the clot has resolved, emboli occluded peripheral renal arteries, or the UAC caused renal arterial spasm or stenosis.

Renal vein thrombosis (RVT) classically presents with gross hematuria, a palpable abdominal mass, and thrombocytopenia and is often associated with hypertension and acute renal failure. Risk factors for RVT include birth asphyxia, maternal diabetes, hypovolemia, sepsis, and indwelling catheters. Most RVTs present within the first 3 days of life and over 70% are unilateral, with a preponderance for the left kidney and male infants (Lau et al. 2007).

Renal arterial stenosis may be a complication of a UAC, or it may be related to fibromuscular



**Table 3** Causes of neonatal and infant hypertension

<b>Renovascular</b>	<b>Neurologic</b>
Renal artery thrombosis	Pain
Renal artery stenosis	Seizures
Renal vein thrombosis	Intracranial hypertension
Mid-aortic syndrome	Familial dysautonomia
Congenital rubella syndrome	Subdural hematoma
Idiopathic arterial calcification of infancy	<b>Endocrine</b>
Renal myofibromatosis	Congenital adrenal hyperplasia
<b>Renal parenchymal</b>	Cushing's syndrome
<i>Congenital</i>	Neonatal hyperthyroidism
Polycystic kidney disease	Hyperaldosteronism
Renal dysplasia	Pheochromocytoma
Unilateral renal hypoplasia	Aldosterone synthase deficiency
Multicystic dysplastic kidney	Argininosuccinate lyase deficiency
Congenital and infantile nephrotic syndrome	<b>Neoplastic</b>
Renal tubular dysgenesis	Neuroblastoma
Atypical hemolytic uremic syndrome	Wilms tumor
<i>Associated with urologic anomaly</i>	Mesoblastic nephroma
Ureteropelvic junction obstruction	Adrenocortical carcinoma
Obstructive uropathy	<b>Medications/drugs</b>
Neurogenic bladder	<i>Maternal</i>
Megaureter	Cocaine
<i>Acquired</i>	Heroin
Acute tubular necrosis	<i>Infant</i>
Cortical necrosis	Corticosteroids
Pyelonephritis	Adrenergic agents
Interstitial nephritis	Caffeine
Nephrocalcinosis	Theophylline
<i>Heritable hypertension</i>	Phenylephrine
Liddle syndrome	Erythropoietin
Apparent mineralocorticoid excess	Pancuronium
Glucocorticoid-remediable aldosteronism	Vitamin D intoxication
<b>Cardiovascular</b>	<b>Other causes</b>
Coarctation of the aorta	Excess salt/saline
Patent ductus arteriosus	Hypercalcemia
Congenital ductus arteriosus aneurysm	Total parenteral nutrition
Congenital aortic aneurysm	Closure of abdominal wall defect

(continued)

**Table 3** (continued)

ECMO	Adrenal hemorrhage
<b>Respiratory</b>	Traction
Chronic lung disease	
Pneumothorax	

dysplasia, mid-aortic syndrome, or external compression by a mass. Less commonly in infants, it may be associated with a vasculitis or disease syndrome such as neurofibromatosis or Williams' syndrome. Other uncommon causes associated with renal artery stenosis include congenital rubella syndrome, renal myofibromatosis, and idiopathic arterial calcification of infancy (Mesner et al. 1966; Kasaragod et al. 1999; Milner et al. 1984). Renal artery stenoses are most commonly unilateral if idiopathic or related to catheters but more commonly bilateral if related to syndromes or other disease processes (see Fig. 4).

### Renal Parenchymal Causes

Renal parenchymal causes may be intrinsic conditions such as polycystic kidney disease or renal dysplasia, may be related to urologic abnormalities such as ureteropelvic junction obstruction or obstructive uropathy, may be acquired conditions such as acute tubular necrosis or cortical necrosis, or rarely may be monogenic forms of hypertension. In hypertensive neonates within the NICU, between 25% and 40% will have a renal abnormality on ultrasound (Seliem et al. 2007; Singh et al. 1992). Lanzarini et al. (2006) studied nephro-urologic malformations in a tertiary care hospital and found an incidence of 0.89% in all infants, with almost 20% of affected neonates developing hypertension during the newborn period.

Congenital renal diseases associated with hypertension include polycystic kidney disease, renal dysplasia in isolation or associated with urologic abnormalities, and renal hypoplasia. Uncommon causes include multicystic dysplastic kidney, congenital or infantile nephrotic syndrome, renal tubular dysgenesis, or atypical hemolytic uremic syndrome. Autosomal recessive

polycystic kidney disease is more often presenting during the neonatal period in the recent decades (Guay-Woodford and Desmond 2003) (see Fig. 5). The median age at diagnosis of hypertension in these patients is 16 days old, and the hypertension may be challenging to treat requiring multiple agents. Even autosomal dominant polycystic kidney disease, where complications

are less common during childhood, can cause hypertension in infants less than 1 year of age (Fick et al. 1993). Multicystic dysplastic kidneys rarely cause hypertension as they are thought to be nonfunctional but in some cases seem to cause severe hypertension, likely renin mediated, where the hypertension resolves after nephrectomy (Abdulhannan et al. 2011).

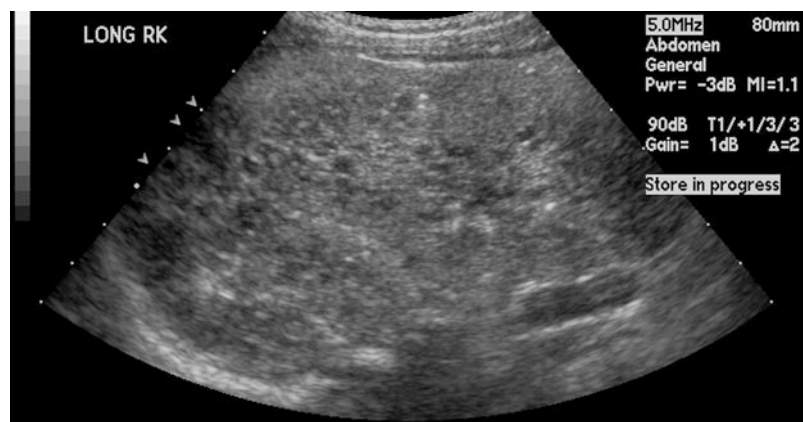
Renal dysplasia may be associated with hypertension and is common in obstructive uropathies such as posterior urethral valve and prune belly syndrome. Renal dysplasia is often not seen in obstruction due to stones or tumors if the obstruction occurs after completion of renal development. Ureteropelvic junction obstruction has been associated with neonatal hypertension where correction of the abnormality is curative in most although infant pyeloplasty has also been related to a postoperative hyperreninemic hypertension (Gilboa and Urizar 1983). Other urologic abnormalities associated with infant hypertension include megaureter and neurogenic bladder, often in infants with a meningomyelocele.

Acquired renal causes of infant hypertension may include acute tubular necrosis related to moderate hypoxic, hypotensive, or nephrotoxic injury to the kidneys, or if more severe, kidneys may develop cortical necrosis. Other acquired causes of renal parenchymal disease and infant hypertension include pyelonephritis, interstitial nephritis, and nephrocalcinosis. Rare heritable forms of hypertension such as Liddle syndrome, apparent mineralocorticoid excess,



**Fig. 4** Renal angiogram demonstrating renal artery stenosis of a second-order renal artery branch with post-stenotic dilation (Pediatric Radiology, Anatomic distribution of renal artery stenosis in children: implications for imaging, volume 36, 2006, pages 1032–1036, Vo NJ, Hammelman BD, Racadio JM, Strife CF, Johnson ND, Racadio JM, with permission of Springer)

**Fig. 5** Renal ultrasound image demonstrating an enlarged echogenic kidney with lack of corticomedullary differentiation and numerous microcysts consistent with autosomal recessive polycystic kidney disease



and glucocorticoid-remediable aldosteronism may present during infancy. Clinical suspicion based on family history and/or suppressed plasma renin can help diagnose these rare causes where treatments are directed at the specific underlying pathophysiology.

### Cardiovascular Causes

Coarctation of the thoracic aorta may present with infantile hypertension and should be suspected in the presence of discrepant arm and leg pulses, perfusion, or blood pressures, especially with a cardiac murmur. Hypertension, as determined by a right upper arm blood pressure measurement, is present in 85% of children with aortic coarctation and persisted in 38% of infants after surgical repair (Smith Maia et al. 2004). This group is also at risk of restenosis and recurrent hypertension during childhood, with systolic blood pressure correlated with residual obstruction as a clue to persistent stenosis (O'Sullivan et al. 2002). Patent ductus arteriosus (PDA), closure of the PDA, and rarely congenital ductus arteriosus aneurysm have all been associated with neonatal hypertension (Murki et al. 2014). The mechanism of the PDA-related hypertension has been suggested to be renal microthrombosis with the PDA as the nidus, while closure of the PDA and hypertension could be related to the use of nonsteroidal anti-inflammatory drugs or the sudden increase in blood volume through the vessels.

ECMO deserves mention as a newer cause of infant hypertension as the technology becomes more widely utilized. An early study showed an incidence of 88% hypertension in infants on ECMO and 44% of infants developed intraventricular hemorrhage (Sell et al. 1987). In this study, 15% of infants still required some form of antihypertensive medication 1 month after ECMO. Other studies have found the incidence of hypertension to vary between 58% and 94%, but fewer hypertensive infants (0–5%) developed intracranial hemorrhage (Boedy et al. 1990; Heggen et al. 2004). A review of 500 neonates treated with ECMO demonstrated that

hypertension is the most common cardiovascular complication, occurring in almost 40% of infants, but when aggressively treated with vasodilators did not adversely affect survival (Becker et al. 1998). The mechanisms are thought to involve alterations in the baroreflex and modulation of hormones.

### Other Causes

Chronic lung disease or bronchopulmonary dysplasia is another common cause of infant hypertension although it may present at neonatal follow-up clinics rather than during NICU admission. Of infants requiring home oxygen therapy for chronic lung disease, the incidence of hypertension during the first year of life has been reported from 13% to 43% with an average age of onset of 4–6 months (Anderson et al. 1993; Abman et al. 1984). Approximately half of cases occur after discharge from the NICU. In addition, some infants with chronic lung disease, or at risk of developing chronic lung disease, are treated with corticosteroids or other medications which can cause or exacerbate hypertension. The exact pathogenesis of the respiratory-related hypertension is unknown but may be related to chronic hypoxemia or hypercapnia, fluid retention, steroids or other medications, or alterations in vascular function or neurohormonal regulation.

Infant hypertension may also be found in disorders of the neurologic system. Pain and seizures may both lead to elevations in blood pressure, but management should be directed at the underlying stimulus, and antihypertensive medications will likely not be necessary. Intracranial hypertension may increase systemic blood pressure. Hypertension occurs in 2–3% of infants with intraventricular hemorrhage (Singh et al. 1992; Blowey et al. 2011). Unfortunately, the clinical signs of systemic hypertension and intraventricular hemorrhage may be indistinguishable and include irritability, lethargy, apnea, hypotonia, seizures, and coma (Adelman 1978). In these situations, appropriate imaging studies may evaluate for central nervous system causes or complications of the high blood pressure.

Although rare, the most commonly associated endocrine etiology for neonatal hypertension is congenital adrenal hyperplasia. Deficiencies in either  $11\beta$ -hydroxylase or  $17\alpha$ -hydroxylase lead to overproduction of deoxycorticosterone which has mineralocorticoid activity. Other endocrine causes of hypertension include Cushing's syndrome, neonatal hyperthyroidism, hyperaldosteronism, and pheochromocytoma.

Several neoplastic causes of infant hypertension have been recognized including Wilms tumor, neuroblastoma, and mesoblastic nephroma which may all present during infancy. The mechanisms for the hypertension may include hyperreninemia related to renal parenchymal compression, renin release by the tumor, compression of the renal vasculature by the mass, or release of catecholamines by the tumor.

Various other causes of neonatal and infant hypertension have been recognized, many of which are iatrogenic. Certain medications or drugs may cause infant hypertension and may be prescribed to infants for a specific indication or related to maternal ingestion, as in cocaine or heroin abuse. Infants with chronic lung disease may be treated with corticosteroids, caffeine, or theophylline, all of which may lead to hypertension. Recent Cochrane reviews of early, moderately early, and late postnatal corticosteroids to prevent chronic lung disease found an increased risk of hypertension regardless of when the steroids were given (Doyle et al. 2014a, b; Halliday et al. 2003). Vitamin D intoxication has been associated with infant hypertension although it is not clear if this is related to hypercalcemia or some other mechanism. Excess saline administration or salt intake may increase blood pressures in neonates. Total parenteral nutrition has also been related to hypertension with the suspected mechanism either salt and water overload or hypercalcemia. Many of these iatrogenic causes of infant hypertension are based on clinically important indications, but when high blood pressures develop, the risk-benefit ratio must be reevaluated to determine if the medication or agent is still deemed essential.

## Evaluation

Many infants with hypertension are asymptomatic, and common symptoms are often nonspecific such as feeding intolerance, vomiting, irritability, or failure to thrive. In those with more obvious symptoms, cardiovascular signs related to the blood pressure can include tachypnea, respiratory distress, and congestive heart failure. In some infants who present with cardiogenic shock, the elevated blood pressure is not detected until after the child is resuscitated and cardiac function improves (Xiao et al. 2013; Louw et al. 2013). Neurologic symptoms may be indistinguishable from intracranial hemorrhage and may include lethargy, apnea, tremors, opisthotonus, facial palsy, hemiplegia, seizures, and coma (Adelman 1978; Deal et al. 1992). Infants may be oliguric or polyuric with renal parenchymal or renovascular abnormalities (Ingelfinger 1982). Clinical signs and symptoms may provide clues to both the severity and the cause of the elevated blood pressure.

The infant's medical history should be reviewed for prenatal exposures, complications of delivery, perinatal course including use of invasive monitoring (umbilical lines), comorbid conditions, and current and previous medications. Family history may be helpful particularly when other infants have had complications in early life or when there is a history of hypertension at a young age. Fortunately, for premature infants, review of the patient chart often reveals the likely cause or several contributing factors to the development of the hypertension.

The initial step in physical assessment of the infant is to confirm the blood pressure elevation by using a standardized blood pressure measurement technique and ensuring the proper cuff size is used (see Table 1). Blood pressures and pulses should be assessed in all four limbs with discrepancies suggestive of coarctation, stenoses, or thromboses. The general condition of the infant should be noted including hydration status and dysmorphic features. Further examination should focus on the differential diagnosis (see Table 3) as well as look for signs of end organ damage including cardiac and neurologic abnormalities. Although procedurally challenging, signs of

**Table 4** Diagnostic investigations for neonatal and infant hypertension

Common investigations	Specific investigations
Serum electrolytes (Na, K, Cl, HCO <sub>3</sub> )	Plasma renin activity, aldosterone
Blood urea nitrogen, creatinine	Head ultrasound
Urinalysis	Serum calcium
Complete blood count	Cortisol, thyroid studies
Renal ultrasound with Doppler	Renal scintigraphy (MAG3, DTPA)
Echocardiography	Angiography

*Na* sodium, *K* potassium, *Cl* chloride, *HCO<sub>3</sub>* bicarbonate, *DTPA-Tc 99m* diethylenetriaminepentaacetic acid, *MAG3-Tc 99m* mercaptoacetyltriglycine

hypertensive retinopathy may be present even in neonates with hypertension (Skalina et al. 1986). Abdominal examination is essential in these infants and should include inspection, auscultation for bruits, and palpation of the size and symmetry of the kidneys and for detection of masses.

Investigations should be tailored to the degree of hypertension and information gathered on history and physical examination. Basic laboratory investigations should include serum electrolytes, blood urea nitrogen, creatinine, urinalysis, and complete blood count (see Table 4). Renal ultrasound with Doppler is a high-yield initial investigation in this population. It is important to note that renal echogenicity and corticomedullary differentiation are relatively increased in neonates (Roth et al. 2003), and therefore interpretation should be conducted by radiologists with experience in pediatrics. Renovascular abnormalities may be suspected on ultrasound when there is abnormal renal size or echogenicity, with Doppler imaging better at identifying a thrombus or stenosis, although lack of vascular anomaly with Doppler ultrasound does not exclude a renovascular cause.

Echocardiography in infants with hypertension may help with diagnosis if cardiac abnormalities are identified but may also demonstrate evidence of target organ damage with left ventricular hypertrophy or congestive heart failure. Hypertension as a cause of heart failure in infants may be suspected by reduced left ventricular systolic function without chamber enlargement, increased left ventricular mass, diastolic dysfunction without left atrial

dilatation, and aortomegaly with increased vascular resistance (Peterson et al. 2006; Louw et al. 2013). Infants may not be hypertensive at presentation when cardiac function is compromised but develop high blood pressure as cardiac function improves. Afterload reduction may improve both blood pressure and cardiac function (Peterson et al. 2006; Louw et al. 2013).

Plasma renin concentration or plasma renin activity may be difficult to interpret with limited normal reference values available for neonates. In addition, various measurements have been used including direct renin, plasma renin activity, and active renin mass with differences in normal values for the different assays. A newborn's renin is higher following a vaginal delivery and is higher in preterm than term infants (Kruger et al. 1998; Richer et al. 1977). In term infants, renin is highest in the first 4 days of life and then levels decrease over the following weeks to months to values similar to older children (Kruger et al. 1998). A suppressed plasma renin may be suggestive of a monogenic form of hypertension, while an elevated renin may suggest a renal artery stenosis or thrombosis. It is important to note that a normal plasma renin is common even in the presence of a renovascular abnormality so clinicians need to be aware of the limitations of this test as a screen for renovascular disease.

When renovascular hypertension is suspected, angiography may be the best investigation but is not always feasible. In children with renovascular hypertension without comorbid conditions, most will have a single stenosis with 75% occurring in a second-order or more distal branch artery (Vo et al. 2006) (see Fig. 4). Digital subtraction angiography is the most accurate for detection of arterial stenoses, and although it is invasive, it may be combined with differential renal vein renin sampling which may be helpful to localize the lesion and guide surgical management. Unfortunately, these procedures require a general anesthetic and may be technically challenging in small infants. Infants are often managed medically until they become an adequate size for the procedure. Other imaging techniques include computed tomography angiography or magnetic resonance angiography, although they are not as good at

detection of intrarenal vascular anomalies which are often present in infants (Roth et al. 2003). Consideration must also be given to a pro-thrombotic workup in infants with proven thromboses as clotting factor abnormalities are common in infants with renal vein thrombosis regardless of other predisposing perinatal conditions (Kosch et al. 2004; Pergantou et al. 2014).

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## Management

### Hypertensive Crises

Hypertensive crises are life-threatening emergencies that require prompt and careful management to avoid complications either of the hypertension or of the treatment. They are best managed within an intensive care setting with intravenous (IV) short-acting antihypertensive agents. Blood pressures should be reduced in a slow, controlled manner over days to avoid severe complications of relative hypotension (Deal et al. 1992). Several classes of antihypertensive agents have been used in infants for management of severe hypertension including vasodilators, ACE inhibitors, calcium channel blockers, and  $\alpha$ - and  $\beta$ -antagonists (see Table 5).

Sodium nitroprusside has been used for decades in hypertensive crises and, due to the very short action of the medication, may be easily titrated to the desired effect. With prolonged use, infants need to be monitored for cyanide toxicity which can occur earlier in infants with renal failure. One case series of IV enalaprilat in neonates demonstrated a high incidence of side effects (Wells et al. 1990). Given the importance of the renin-angiotensin-aldosterone system (RAAS) in neonates, and lack of established dose, it cannot be recommended. Nicardipine, a dihydropyridine calcium channel blocker, has been used safely and effectively in premature and term infants with hypertension but requires administration through a central venous line and should be avoided in perinatal asphyxia (Milou et al. 2000; Flynn et al. 2001). Labetalol is a selective  $\alpha$ -1-adrenergic

antagonist and nonselective beta-adrenergic antagonist that has been used for decades to treat hypertensive crises. The efficacy and safety of IV labetalol is comparable to IV nitroprusside or IV nicardipine in infants less than 24 months of age (Thomas et al. 2011). Side effects of labetalol included hypoglycemia, bradycardia, and hypotension, and caution must be used in patients with preexisting brain injury. Esmolol, an IV cardioselective short-acting beta-antagonist, is a newer agent but has been used in children undergoing cardiac surgery for repair of congenital anomalies with good safety and efficacy (Wiest et al. 1998; Tabbutt et al. 2008).

Unfortunately, there are occasions when intravenous infusions are not immediately available and other agents must be used. Hydralazine may be given IV with a short onset of action of 5–20 min or orally with effect starting in 20–30 min. Nifedipine has been studied in infants with hypertensive crises at a dose of 2.5 mg with good effect (Lopez-Herce et al. 1989). Caution must be used with this medication as others have found transient neurologic changes in children and small doses require extraction of the liquid from a capsule with estimation of dose. Isradipine is a newer calcium channel blocker that is being used for acute hypertension as it is available in an immediate release formulation with onset of action of 30–60 min (Miyashita et al. 2010; Flynn and Warnick 2002). Other fast-acting medications to consider include oral captopril, clonidine, and minoxidil (see Table 5). Some of these agents may not be available in all locations, so one's choice of agent may be partly driven by what is available.

### Non-emergent Hypertension

As with many medications in pediatrics, most antihypertensive drugs are not approved for use in infants, as adequate studies have not been conducted involving this age group. In neonates, the physiology of the immediate postnatal life is very different from older children, and therefore,

**Table 5** Antihypertensive medications and recommended dosages for neonatal and infant hypertension

Drug class	Medication and route	Dose	Interval	Comments
Direct vasodilators	Sodium nitroprusside (IV)	Initial: 0.25 mcg/kg/min Max: 8 mcg/kg/min	Infusion	May cause hypotension, tachycardia. Monitor for cyanide toxicity. Caution in renal failure
	Hydralazine (IV) (PO)	0.2–1.0 mg/kg/dose 0.25–1.0 mg/kg/dose Max: 7 mg/kg/day	Q 4–6 h TID to QID	May cause tachycardia, fluid retention, diarrhea, emesis, agranulocytosis
	Minoxidil (PO)	0.1–1.0 mg/kg/day	BID	May cause tachycardia, fluid retention, hypertrichosis, pericardial tamponade, anorexia
ACE inhibitors	Captopril (PO)	Neonates Initial: 0.01 mg/kg/dose Max: 2 mg/kg/day Infants Initial: 0.1–0.3 mg/kg/dose Max: 6 mg/kg/day	BID to TID	May cause hypotension, oliguria, acute renal failure, hyperkalemia, neurologic complications
	Enalapril (PO)	Neonates: 0.04–0.1 mg/kg/day Infants: 0.08–0.6 mg/kg/day	Daily Daily to BID	All may cause hypotension, oliguria, acute renal failure, hyperkalemia, agranulocytosis, angioedema. Caution in preterm neonates
	Lisinopril (PO)	Infants: 0.07–0.5 mg/kg/day	Daily	
Calcium channel blockers	Nicardipine (IV)	0.5–4 mcg/kg/min	Infusion (central line)	May cause hypotension, tachycardia, and flushing. Caution in perinatal asphyxia
	Amlodipine (PO)	Initial: 0.05 mg/kg/dose Max: 0.6 mg/kg/day	Daily to BID	May cause edema, tachycardia, gingival hypertrophy
	Isradipine (PO)	Initial: 0.05–0.15 mg/kg/dose Max: 0.8 mg/kg/day	TID to QID	May cause hypotension, tachycardia, edema. Caution with QTc prolongation
	Nifedipine (PO)	0.1–0.25 mg/kg/dose Max: 2.5 mg	Q 4–6 h	May cause hypotension, tachycardia, transient neurologic changes
$\alpha$ - and $\beta$ -antagonists	Labetalol (IV)	0.2–1.0 mg/kg/dose 0.25–3.0 mg/kg/h	Load Infusion	May cause hypotension, bradycardia, hyperkalemia, hypoglycemia, hyperglycemia, edema. Caution in chronic lung disease, heart block, unstable heart failure
	Labetalol (PO)	1.0–10 mg/kg/day	BID	
	Carvedilol (PO)	0.05–0.4 mg/kg/dose	BID to TID	
$\beta$ -Antagonists	Esmolol (IV)	50–1,000 mcg/kg/min	Infusion	All may cause hypotension, bradycardia. Caution in chronic lung disease, unstable heart failure
	Propranolol (IV)	0.01–0.15 mg/kg/dose	QID	
	Propranolol (PO)	0.25–5 mg/kg/day	TID to QID	
$\alpha$ -Antagonist	Prazosin (PO)	Initial: 5 mcg/kg/dose 0.05–0.5 mg/kg/day	TID	May cause hypotension, somnolence

(continued)

**Table 5** (continued)

Drug class	Medication and route	Dose	Interval	Comments
Central $\alpha$ -agonist	Clonidine (PO)	2–10 mcg/kg/day	QID	May cause hypotension, bradycardia, rebound hypertension, somnolence, xerostomia
Diuretics	Amiloride (PO)	0.4–0.625 mg/kg/day	Daily to BID	May cause hyperkalemia. Caution in renal failure
	Furosemide (PO)	1–6 mg/kg/dose	Daily to QID	May cause hyponatremia, hypokalemia, ototoxicity, nephrocalcinosis
	Hydrochlorothiazide (PO)	1–3 mg/kg/day	Daily to BID	May cause hyponatremia, hypokalemia, alkalosis
	Spironolactone (PO)	1–3 mg/kg/day	Daily to BID	May cause hyperkalemia. Caution in renal failure

ACE angiotensin-converting enzyme, BID twice daily, IV intravenous, PO oral, QID four times daily, TID three times daily

drug dosages and side effects can be quite different. Many older antihypertensive drugs have been used for decades to treat infant hypertension and are unlikely to be formally studied.

Captopril, a short-acting ACE inhibitor, is much more potent in neonates, and they require a lower dose for clinical effect (see Table 5). Infants may experience a significant decrease in blood pressure associated with captopril as well as acute renal failure and neurologic consequences (Perlman and Volpe 1989). Similar caution should be used for longer-acting ACE inhibitors such as enalapril and lisinopril when used in infants. In addition, we are learning more about the importance of the RAAS during renal development (Lacoste et al. 2006). Concerns have been raised about persistent use of inhibitors of this developmentally important system in neonates as long-term consequences have yet to be studied.

Amlodipine, a third-generation dihydropyridine calcium channel blocker, is generally safe and effective for management of childhood hypertension. It can be compounded in a suspension for use in young children and has a long half-life although may need to be dosed twice daily in younger children (Flynn and Pasko 2000). Isradipine, a second-generation dihydropyridine calcium channel blocker, has been used in hospitalized neonates, infants, and children with good effect (Miyashita et al. 2010; Flynn and Warnick 2002). Dosage based on size produced a relatively larger decrease in blood pressure in the infants compared to older children, but only 1% of patients developed

clinically significant hypotension. Isradipine can be compounded into a stable suspension preparation improving its utility in neonates and infants.

$\alpha$ - and  $\beta$ -antagonists have been available and used for management of infant hypertension for decades but have been rarely studied in this population. The  $\beta$ -blocking side effects may include bradycardia, hyperglycemia, and hyperkalemia. Caution must be used in infants with chronic lung disease and heart block. Diuretics are used commonly in NICUs, often for indications other than blood pressure. They have modest effects on blood pressure reduction but may be first-line agents in infants with chronic lung disease or fluid retention. Electrolyte abnormalities are not uncommon and require laboratory monitoring.

Although most antihypertensive medications are not approved for use in infants, physicians have had to treat blood pressure with various agents to prevent the complications of uncontrolled hypertension. Hydralazine has been the most commonly used medication for neonatal hypertension since the 1970s. Other commonly prescribed agents include calcium channel blockers and ACE inhibitors with alpha- and beta-blockers less common but still of use (Seliem et al. 2007; Blowey et al. 2011; Sahu et al. 2013). Of interest, 30–50% of infants require more than one medication for blood pressure control, and this seems more common in term neonates. The hypertension may also be persistent with 40–85% of infants on antihypertensive medications at the time of discharge from the NICU. Of concern, in recent studies, 18–26% of identified hypertension



was not treated with any antihypertensive medications (Seliem et al. 2007; Blowey et al. 2011). The reasons were not identified but could be related to uncertainty in accurate diagnosis, lack of visible consequences of the hypertension, or unfamiliarity with antihypertensive medications, dosing, and side effects in neonates and infants.

In less than 10% of cases, surgical or interventional management can be curative for hypertension in infants (Sahu et al. 2013). For renal artery stenosis, percutaneous transluminal renal angioplasty to correct the stenosis may be curative when the lesion is unilateral although the procedure is technically more difficult in small infants who are often managed medically awaiting further growth. Surgical correction of coarctation of the thoracic aorta improves blood pressure in many but not all infants with this congenital malformation. For infants with tumors such as Wilms tumor, neuroblastoma, and mesoblastic nephroma, surgery usually results in normalization of the blood pressure. Rarely structural or function anomalies of the kidney and urinary tract associated with severe hypertension may require surgery. It has been reported as curative in some cases of ureteropelvic junction obstruction, multicystic dysplastic kidney, and unilateral renal hypoplasia (Munoz et al. 1977; Abdulhannan et al. 2011; Tokunaka et al. 1987). In exceptional circumstances, nephrectomy has been used for management of hypertension related to autosomal recessive polycystic kidney disease, which is often difficult to treat in infants, although may become easier with time (Roy et al. 1997).

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### Long-Term Outcome

Few follow-up studies of neonatal hypertension have been published. The review published by Adelman (1978) of 17 infants with neonatal hypertension found that 13 (76%) were normotensive off antihypertensive medications by 3–6 months after the onset. Results were similar in a slightly later study of NICU hypertensive infants where more than 50% were normotensive within the first month of life, two-thirds by 6 months of age, and more than 80% by 1 year of age (Buchi and Siegler 1986). In a recent Australian study of neonates with hypertension,

more than 40% of infants were still receiving antihypertensive medications at discharge and 15% were still on treatment at follow-up at 3–6 months of age (Seliem et al. 2007). The vast majority seem to undergo resolution of their hypertension in the first 1–2 years of life (Shah et al. 2015).

While most neonatal hypertension improves with time, some conditions are associated with increasing rates of hypertension. Follow-up of infants with chronic lung disease has shown that half of the hypertension develops after NICU discharge and can last for up to 2 years (Anderson et al. 1993). In children with autosomal recessive polycystic kidney disease who survive the neonatal period, almost 40% require antihypertensive medications by 1 year, 50% by 3 years, and 60% by 15 years of age (Roy et al. 1997). Several long-term studies of renal vein thrombosis during infancy have found kidney outcomes are poor regardless of treatment with around 70% showing irreversible kidney damage at follow-up and about 20% of these patients had elevated blood pressure in the long term (Lau et al. 2007).

The recommendation of the 4th Report (2004) of the National High Blood Pressure Education Program is that children under 3 years of age only have their blood pressure measured at clinic visits if they have conditions associated with hypertension (e.g., cardiac or kidney disease) or if they were premature, VLBW, or NICU graduates. Sheftel et al. (1983) screened infants at follow-up clinics who were normotensive during their NICU course and found 9% were persistently hypertensive. After extending their cohort and follow-up period, they found 2.6% were hypertensive at an average follow-up of 19 months (Friedman and Husted 1987). Causes identified included ureteropelvic junction obstruction, renal artery thrombosis, coarctation of the aorta, and neuroblastoma, but no cause was identified in the majority of children.

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### Neonatal Risk Factors for Later Renal and Cardiovascular Disease

It is becoming more widely recognized that perinatal events may alter risks for renal and cardiovascular disease in adolescence and adulthood.

A few comments are included here, but for a more detailed review, see ► [Chap. 8, “Perinatal Programming of Arterial Pressure.”](#) In particular, there has been much focus recently on prematurity, intrauterine growth restriction, and postnatal weight gain as risk factors for future renal and cardiovascular disease. Although, there is still much controversy in the literature regarding which factors have a role and how much of an effect perinatal factors have compared to later health status.

The risks for development of hypertension in this population are likely multifactorial as these infants are often born prior to completion of nephrogenesis, at about 36 weeks gestation, and may be susceptible to acute kidney injury from hypoxia, hypotension, and nephrotoxins in addition to a possible genetic predisposition. Rodriguez et al. (2004) examined renal autopsy specimens from premature and term neonates and found that glomerulogenesis correlates with gestational age and is decreased in all preterm infants. In addition, active glomerulogenesis is absent in longer surviving premature infants and is further inhibited by acute kidney injury. Brenner et al. (1988) hypothesized that reduced nephron endowment predisposes to the development of hypertension through altered renal hemodynamics and reduced salt excretion (Brenner et al. 1988). They further postulated that with reduced nephron number, somatic growth can exceed renal growth and compensation mechanisms and one of the consequences may be hypertension (Mackenzie et al. 1996).

Studies that have followed up premature infants through childhood have found an increased incidence of hypertension, chronic renal insufficiency, and tubular dysfunction in this population (Kistvan Halthe et al. 2007). The renal dysfunction may be more marked in the presence of proteinuria and obesity (Abitbol et al. 2009). Using ambulatory blood pressure monitoring (ABPM), it was found that children born prematurely, particularly those that had intrauterine growth restriction, had higher nocturnal blood pressures and reduced dipping compared to controls (Bayrakci et al. 2007). Young adults who were born very premature (<32 weeks) or at very low birth weight

(<1,500 g) have a very high rate of prehypertension (approx. 40%) and a higher prevalence of hypertension (approx. 10%) when compared to the general population of a similar age (Keijzer-Veen et al. 2005). As discussed above, hypertension may develop in children and adults who were born premature due to a reduced nephron endowment and maladaptive compensatory mechanisms.

Several studies have shown that low birth weight or being born small for gestational age is inversely correlated with blood pressure in childhood and early adulthood and is associated with a higher prevalence of hypertension (Hovi et al. 2010; de Jong et al. 2012; Zamecznik et al. 2014). A large cohort study including almost 30,000 children found that placental ratio percentage, as an indicator of intrauterine growth restriction, was a predictor of elevated blood pressure at 7 years of age while unadjusted birth weight was not (Hemachandra et al. 2006). ABPM studies in children born SGA have found blunted circadian and ultradian rhythms in addition to elevated blood pressures and hypertension when compared to appropriate birth weight children (Wolfenstetter et al. 2012; Zamecznik et al. 2014). Children and adolescents born SGA or growth restricted have lower elasticity of large and small blood vessels but a stronger vasodilatory response to ischemia compared to appropriate for gestational age children (Strambi et al. 2012). Differential vascular programming and altered cardiovascular regulation may be influencing later cardiovascular risks.

The role of early weight gain in later development of cardiovascular disease is still under debate. Studies have shown that accelerated infant weight gain during the first several months of life is related to higher systolic blood pressure as well as abnormal lipid profile and glucose metabolism during childhood and adolescence (Belfort et al. 2007; Fabricius-Bjerre et al. 2011; Lurbe et al. 2014). Another study of children who were born premature also showed that increased weight gain over the first year was associated with a slightly higher systolic blood pressure in childhood, but the weight gain was also associated with improved neurocognition (Belfort et al. 2010).

Several other studies have shown that early postnatal growth has an influence on childhood and early adulthood blood pressures but that the effect is small compared to later childhood growth or current body mass index (Keijzer-Veen et al. 2005; Law et al. 2002; Jones et al. 2012; Howe et al. 2014). This has led to the suggestion that the focus shift from perinatal growth to prevention of adiposity from later infancy through childhood as a more effective mechanism to reduce adulthood cardiovascular disease.

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## Conclusions

Neonatal and infant hypertension may be a challenging clinical issue, primarily because we are not certain of the definition of hypertension within this population and limited medication studies are available to guide treatment. Various factors, both intrinsic and extrinsic, can influence neonatal blood pressures with the strongest determinants being birth weight, gestational age, and postmenstrual age. Newer data on normal blood pressure values are available based on stable infants, but larger multicenter studies are needed to confirm and refine these reference values. The incidence of neonatal hypertension has remained fairly consistent over the last 30 years at 1–2% despite changes in the complexity of the neonatal population with new technologic advances. There seems to be a difference in the etiology of hypertension between preterm and term infants. Most causes or risk factors can easily be determined by assessment of the infant and some basic investigations. Neonatal hypertension is undertreated in the NICU and the reasons for this need further exploration. Most neonatal hypertension will resolve in the first 1–2 years although some disease states identified during infancy are associated with the development of hypertension over time. The exact impact of perinatal events on later renal and cardiovascular disease is still under investigation, but appropriate management of neonatal and infant hypertension is important for both the short- and long-term health of these infants.

## Cross-References

- ▶ [Development of Blood Pressure Norms and Definition of Hypertension in Children](#)
- ▶ [Management of Hypertensive Emergencies](#)
- ▶ [Methodology of Casual Blood Pressure Measurement](#)
- ▶ [Perinatal Programming of Arterial Pressure](#)
- ▶ [Pharmacologic Treatment of Pediatric Hypertension](#)
- ▶ [Renovascular Hypertension, Vasculitis, and Aortic Coarctation](#)
- ▶ [Secondary Forms of Hypertension in Children: Overview](#)

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## Abstract

Sleep is a vital physiologic phenomenon that involves multiple processes such as regulation of breathing during sleep. In children, sleep-disordered breathing results in daytime impairment, cognitive-behavioral problems, as well as cardiovascular effects. The relationship between obstructive sleep apnea (OSA) and systemic hypertension (HTN) is not well defined in children. There is growing evidence to suggest an association between these two conditions, particularly when blood pressure is measured during sleep, and even long-term follow-up data regarding OSA and BP in youth. There is also some evidence suggesting an independent effect of OSA on left ventricular geometry changes which has been shown to improve after treatment of OSA. Certainly, obesity is a factor in the associations between OSA, HTN, and left ventricular geometry changes. The interaction and causal relationship is still unknown, but recent studies are

adding to the literature to inform this interaction. Therefore, the National High Blood Pressure Education Program Working Group recommends screening for OSA as a comorbid condition in children with HTN.

## Keywords

Obstructive sleep apnea • Blood pressure • Hypertension • Children • Sleep-disordered breathing

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## Introduction

Sleep-disordered breathing (SDB) encompasses all forms of respiratory abnormalities during sleep. SDB involves a spectrum ranging from primary snoring to the most severe form being obstructive sleep apnea (OSA). OSA has been linked to various co-morbid conditions such as cerebral and cardiovascular disorders such as systemic hypertension. In adults, the relationship between OSA and hypertension has been well documented. Long-standing untreated OSA has been associated with drug resistant hypertension. Therefore, patients with hypertension are typically screened for OSA. Similar to the adult population, the National High Blood Pressure Education Program Working Group (2004) and the American Academy of Pediatrics (Flynn et al. 2017) have recommended screening children with hypertension for OSA. The relationship between OSA and hypertension is not well established but has started to become more recognized in children. There are increasing studies linking OSA to hypertension but the actual mechanism has yet to be defined. The purpose of this chapter is to review the clinical symptoms and pathophysiology of pediatric OSA as well as to present the most updated data of OSA in relation to systemic hypertension in children.

## Definitions and Epidemiology of SDB

Sleep-related breathing disorders are a group of disorders which are characterized as any abnormality in respiration during sleep. This includes obstructive sleep apnea, central sleep apnea syndromes, sleep-related hypoventilation disorders, and sleep-related hypoxemia disorders (Table 1). For some individuals, there may be overlap and may meet the diagnostic criteria for more than one of the disorders. For the purposes of this chapter, the focus will remain on the group of obstructive sleep apnea disorders.

There are few data that clearly define the different variations of sleep-related breathing disorders. Therefore, it is commonly viewed as a spectrum ranging from a mild form of primary snoring to the most severe form of OSA with

**Table 1** Summary of pediatric sleep related breathing disorders

<b>Snoring</b>	Respiratory sound generated by upper airway
<b>Obstructive sleep apnea</b>	Repetitive episodes of complete or partial upper airway obstruction during sleep; results in disruption of ventilation and/or sleep pattern
<b>Central sleep apnea</b>	Cessation of airflow during sleep associated with an absence of respiratory effort
<b>Sleep-related hypoventilation</b>	Abnormally elevated arterial partial pressure of CO <sub>2</sub> greater than 50 mmHg during sleep for 25% or more of the total sleep time
<b>Sleep-related hypoxemia</b>	Arterial oxygen saturation during sleep is less than or equal to 90% for greater than or equal to 5 min in duration

abnormalities in ventilation. Primary snoring is defined as frequent inspiratory sound produced by the vibration of the upper airway during sleep. Snoring is a respiratory sound that is generated in the upper airway during inspiration. Primary snoring is not associated with disruption in ventilation, fragmented sleep, or daytime symptoms. The incidence of snoring in children is about 10–12% (Sateia et al. 2014). Oftentimes, snoring can be the only symptom reported by the caregiver indicating a form of sleep-related breathing disorder. Snoring is a core symptom of obstructive sleep apnea. Therefore, the report of snoring typically prompts a diagnostic work up to distinguish primary snoring from a more severe form of sleep-related breathing disorder.

Upper airway resistance syndrome (UARS) falls under the category of obstructive sleep apnea. Upper airway resistance syndrome is characterized by increasing negative intrathoracic pressures during inspiration that leads to nocturnal awakenings or arousals (Gold et al. 2002). The events are independent of complete upper airway obstruction, partial upper airway obstruction, or oxygen desaturations. However, the events can lead to daytime symptoms. Studies have shown that the pathophysiology of upper airway resistance is not much different than OSA and thus the use of UARS has slowly declined and been replaced with OSA.

Obstructive sleep apnea (OSA) is also known as sleep apnea, upper airway obstruction, and Pickwickian syndrome. It has been well described as early as 1976 (Guilleminault et al. 1976). OSA is characterized by intermittent complete or partial obstruction of the upper airway. Apneas in children are defined as a 90% decrease of airflow in comparison to the baseline breath for two breaths and is associated with a presence of respiratory effort throughout the entire period of absent air flow. Hypopneas in children are defined as 30% decrease in airflow in comparison to the baseline breath for two consecutive breaths and are associated with a 3% drop in oxygen saturation or arousal. If the criteria for an obstructive apnea or hypopnea are not met but there is an interruption of airflow and increase in respiratory effort followed by an arousal, then the event is labeled as a respiratory effort related arousal (RERA).

Based on these definitions, two values can be calculated – the apnea hypopnea index (AHI) and respiratory disturbance index (RDI). The AHI is the calculated number of apneas and hypopneas per hour of sleep. In children, an AHI greater than 1 per hour of sleep is diagnostic of OSA. The AHI does not include respiratory effort related arousals (RERAS). Therefore, the RDI is also used by clinical practitioners to account for all respiratory events during sleep. The RDI is a total of apneas, hypopneas, and RERAS per hour of sleep. An RDI of greater than 1 per hour of sleep is diagnostic of OSA in children. The AHI and RDI both include central apneas. Central apneas are scored as absence of airflow in conjunction with absence of inspiratory effort. Therefore, when reviewing the severity of obstructive sleep apnea, the central apneas are removed resulting in an obstructive AHI (OAHI) and obstructive RDI (ORDI).

## Clinical Presentation

Children with OSA may present with various symptoms during sleep as well as symptoms during the day (Table 2). OSA can present at any age. The most common symptom is snoring. The snoring can be loud and intermittent. There is no correlation between the loudness and intensity

**Table 2** Clinical symptoms of pediatric obstructive sleep apnea

Snoring
Difficulty breathing while sleeping
Witnessed apneas/pauses in breathing
Paradoxical breathing
Frequent awakenings/restless sleep
Sweating during sleep
Posturing to promote airway patency/sleeping on multiple pillows
Secondary enuresis
Chronic mouth breathing
Morning headache
Behavior/learning/attention problems
Daytime somnolence

of snoring to the severity of OSA (American Academy of Pediatrics, Section on Pediatric Pulmonology, Subcommittee on OSA 2002). Oftentimes, snoring is only audible by caregivers during colds or during periods of significant nasal congestion. Caregivers with infants or small children may report periods of noisy breathing during sleep.

In addition to snoring, the next common symptom of OSA is difficulty with breathing during sleep. Caregivers may often witness the snoring be accompanied by periods of apnea or pauses in breathing. Children have a compliant rib cage which contributes to thoracoabdominal asynchrony, commonly known as paradoxical breathing. Thoracoabdominal asynchrony may be common in children up to 2–3 years of age, particularly during rapid eye movement (REM) sleep. However, it may be the only presenting symptom in children with neuromuscular weakness, such as in children with muscular dystrophy. Therefore, routine polysomnography to screen for sleep-disordered breathing in children with neuromuscular weakness is indicated even without clinical symptoms (Kushida et al. 2005).

The interruption in airflow can be associated with frequent movements during sleep or awakenings from sleep all of which can fragment sleep. Oftentimes, the child will sleep in multiple positions during the night thus caregivers will often report that the child is restless during sleep. As a result of the restless sleep or fragmented sleep,

children will have daytime symptoms. Caregivers of infants and children will report behavioral problems, hyperactive behavior, moodiness, irritability, and impaired school performance (Melendres et al. 2004). Excessive daytime sleepiness may be another reported symptom but is more common in older children and young adults. Other symptoms include mouth breathing, morning headaches, recurrent respiratory infections, and nocturnal sweating.

Nocturnal enuresis has been noted to be associated with OSA. It has been reported in 8–47% of children with OSA (Brooks and Topol 2003). Studies have shown that hormonal dysregulation and increased levels of catecholamines as a result of frequent arousals may be a contributing factor. Enuresis associated with OSA often resolves after successful treatment of sleep-disordered breathing (Weider et al. 1991).

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## **Etiology and Prevalence of OSA in Children**

OSA can occur at any age – from the neonatal period to adulthood. In prepubertal children, OSA is equally common in boys and girls whereas it is more common in adolescent boys than girls. The etiology of OSA in children is suspected to be a combination of various factors. However, there seems to be a bimodal distribution in regard to prevalence of OSA in children. The first peak occurs in school age children 2–8 years of age. The prevalence of OSA in school age children ranges from 1 to 4% but may be much higher as a result of the recent obesity epidemic (Verhulst et al. 2007). This is mainly in part due to enlarged lymphoid tissue of the tonsils and adenoids. Adenotonsillar hypertrophy and obesity are the most common predisposing factors in developing OSA. Adenotonsillar hypertrophy is more common in younger children as there is a progressive increase in lymphoid tissue until pubertal age. The degree of tonsillar hypertrophy has not been associated with more significant OSA (Wang et al. 1998).

The second peak occurs during adolescence as a result of increased weight gain. There is limited

data on the prevalence of OSA in adolescents and in infants. As a result of the recent obesity epidemic, obesity has progressively increased thus contributing to rising prevalence of OSA in children. The risk for residual OSA in children who have undergone adenotonsillectomy is greater in obese children (Chervin et al. 2000).

Review of family history during clinical evaluation may indicate a genetic component in the development of OSA in children. First-degree relatives with OSA increase the risk by 2–3 fold. The exact link is not well defined and may be related to the heritability of predisposing conditions such as obesity. Genetic syndromes are also associated with developing OSA due to loss of neuromuscular control during sleep.

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## **Diagnostic Testing for OSA**

Due to the increasing incidence of OSA in children, various screening methods are available to identify those with a high risk of developing OSA. History by the caregiver involves screening with symptoms suggestive of OSA. Physical examination includes identifying tonsillar hypertrophy as well as craniofacial abnormalities. This includes retrognathia, micrognathia, cleft lip/palate, features of chronic allergic rhinitis, etc. In addition, physical examination should also assess for hypotonia and for muscle weakness. This is particularly important in children with syndromes such as Down syndrome, Prader-Willi syndrome, etc. (Table 3).

The gold standard in establishing the diagnosis of sleep-related breathing disorders is overnight polysomnography (PSG). Overnight PSG can be performed in all age ranges. The American Academy of Sleep Medicine (AASM) established pediatric scoring rules for sleep studies in children 2 months post term and older. However, normative values in determining the severity of OSA have not been well established. An AHI greater than 1 per hour is diagnostic of obstructive sleep apnea in children. In children ages 13–18 years of age, adult diagnostic values can be applicable. Children typically experience more obstructive hypopneas or RERAS in comparison to adults. Therefore, there

**Table 3** Medical conditions predisposed to developing pediatric OSA

Obesity
Down syndrome
Prader Willi syndrome
Achondroplasia
Cerebral palsy/global developmental delay
Neuromuscular disease
Crouzon's syndrome
Treacher Collins syndrome
Apert syndrome
Pfeiffer's syndrome
Mucopolysaccharidosis (i.e., Hunters, Hurlers)
Pierre Robin sequence
Chiari malformation

are variations in classifying the severity of OSA in children and the AHI may underestimate the severity of sleep-disordered breathing.

The utility of home sleep apnea testing (HSAT) in adults is well defined. Several studies have shown HSAT in children to be feasible; however, the reproducibility of the data recorded may not be as beneficial and interpretable (Tan et al. 2015). Therefore, HSAT is currently not approved in children under 18 years of age. It has been used on a case-by-case basis. Currently, there are several studies underway with the intent to validate HSAT in certain pediatric patients.

There are several well-established questionnaires available in identifying OSA in adults based on symptomatology and comorbidities. However, there are limited questionnaires solely for pediatric use. Most adult questionnaires have been altered to apply to the pediatric population, such as the modified STOP BANG questionnaire. This questionnaire incorporates the presence of snoring, tonsillar hypertrophy, daytime sleepiness symptoms, observed obstruction, behavioral problems, BMI, age at diagnostic screening, presence of neuromuscular disorder, and presence of genetic/congenital disorder. Overall, studies have shown this questionnaire to be useful in identifying high-risk adolescents with OSA (Combs et al. 2015). The pediatric sleep questionnaire (PSQ) is a 22-item questionnaire that has been strongly associated in identifying sleep disordered breathing in children 2–18 years of age (Chervin et al. 2000).

The majority of the questionnaires used in the pediatric population have come from adult studies and thus do not account for various mechanisms specific to pediatrics such as puberty, craniofacial abnormalities, etc.

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## Pathophysiology of OSA

The pathophysiology of OSA in children is complex and not well understood. During sleep, there is an increase in resistance of the upper airway. The combination of the increased resistance and increased muscle tone contribute to the reduction of the upper airway. Children typically have obstruction of the oropharynx and hypopharynx secondary to large tonsils and adenoids. This has been confirmed via MRI of the upper airway (Arens et al. 2001). In addition, there is a reduction in functional residual capacity of the lung volumes during REM sleep. This in part is related to narrowing of the airway diameter as well as decreased pharyngeal tone. The normal decrease in muscle tone during REM sleep contributes to a more rapid decrease in oxygen saturation with apnea or hypopneas. In addition, during normal sleep, the ventilatory drive is slightly blunted in response to the hypoxemia and hypercapnia. The ventilatory drive typically regulates the tone of the upper airway.

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## Obstructive Sleep Apnea and Hypertension

### Pathophysiology

The pathophysiology of OSA and HTN is complex and multifactorial, and often confounded by comorbidities. A majority of what is known comes from studies conducted in adults. There is substantial evidence the autonomic nervous system (ANS) has a significant influence in the relationship between OSA and HTN, but other factors have been identified, including vasoactive substances, endothelial dysfunction, and intrathoracic changes. The ANS regulates the cardiovascular system via changes in the heart rate,

cardiac output, and vascular resistance with a balance between sympathetic and parasympathetic activity via the baroreflex. When arterial pressure increases, parasympathetic signaling to the heart results in a decreased HR to maintain BP and offset the increased arterial pressure. Decreases in arterial pressure activate the sympathetic nervous system (SNS) leading to increased HR and increased peripheral vascular resistance which again restores BP. The SNS can also be activated by hypoxia or hypercapnia via chemoreceptors with the same effect on HR and BP, but rather than a restoration of BP, there is now an increase in BP (Nisbet et al. 2013). Normally, during sleep, heart rate, BP, and sympathetic activity decline, but intermittent hypoxemia, hypercapnia, and arousals activate the SNS, causing elevations in BP and HR which can persist into wakefulness (Malhotra and Loscalzo 2009; Somers et al. 1995). The long-term effect of these intermittent surges in sympathetic activity is thought to reset the baroreflex or baroreceptor sensitivity leading to sustained, chronic elevations in BP (Nisbet et al. 2013). A few studies in children using noninvasive measurements of the SNS have supported the role of the ANS in the relationship between OSA and HTN (Gozal et al. 2013).

Other measures of sympathetic activity in children have included urinary catecholamines measured in timed urine collections (Kaditis et al. 2009; Kelly et al. 2010). These studies have shown significantly elevated catecholamine levels (primarily norepinephrine or normetanephrine) associated with an elevated obstructive AHI. There have been other vasoactive substances found to correlate with OSA in adults such as endothelin (Gjorup et al. 2007) and nitric oxide (Phillips et al. 1999) which are believed to contribute to endothelial dysfunction. In response to nocturnal hypoxemia, an altered production of these substances by the endothelial cells (decreased nitric oxide and increased endothelin-1) results in vasoconstriction. In children, one study found lower nitric oxide levels in those with OSA and moderate to severe hypoxemia suggesting endothelial dysfunction similar to adults (Kaditis et al. 2010). Another study comparing endothelin levels in children with OSA pre- and postadenotonsillectomy

found a significant decrease in endothelin postsurgical intervention (Tatlipinar et al. 2011).

Lastly, shifts in the intrathoracic pressure in patients with OSA due to respiratory effort against an occluded airway are thought to affect the ANS, and also have a direct effect on the heart. The negative intrathoracic pressure created with sustained breathing efforts during upper airway obstruction leads to activation of the SNS and ultimately, increased BP (Malhotra and Loscalzo 2009). Additionally, the negative intrathoracic pressure affects the transmural gradient across the atria, ventricles, and aorta which may remodel the cardiac ventricle. Left ventricular transmbrane pressure is a reflection of the afterload on the left ventricle. Elevated left ventricular transmbrane pressures were detected during the ventilatory period following an obstructive apnea in adults with congestive heart failure (Tkacova et al. 1998). In control patients (adults with normal BMI and no history of OSA or heart disease), Orban et al. simulated the increased negative intrathoracic pressure of OSA. As a result of the increased negative intrathoracic pressure alone (without associated hypoxemia or sleep arousals), they demonstrated decreased left atrial volume and decreased left ventricular systolic function reflecting an increase in left ventricular afterload (Orban et al. 2008). This increase in cardiac afterload following obstructive apneas may explain the presence of left ventricular hypertrophy (LVH) in patients with OSA independent of BP (Hedner et al. 1990).

### **Association Between OSA and HTN**

As with many studies regarding BP in children, the manner in which BP is analyzed or even measured varies in studies investigating BP and OSA. Some studies measured casual BP either with oscillometric devices, calibrated sphygmomanometers, or mercury manometers. Other studies measured BP overnight either intermittently using oscillometric devices or continuously using finger photoplethysmography. The remaining studies measured ambulatory blood pressure (ABP) during wake and sleep. Most of the studies analyzed raw

BP values for systolic, diastolic, and/or mean arterial BP separately, but some studies indexed BP to the 95th percentile according to various reference values. The definitions of hypertension also varied among the studies. Studies were only included in this chapter if OSA was evaluated by an overnight PSG. Of those studies, participants were mostly divided into two or three groups depending on AHI or snoring. Some studies had a control group without any symptoms, others used primary snorers with an  $AHI < 1$  for the control group, and one study only included patients with OSA. A few studies evaluated BP in relation to the different sleep stages.

Guilleminault et al. first brought attention to the presence of HTN in children with OSA, reporting a case series of five out of eight children with both sleep apnea and HTN (Guilleminault et al. 1976). Subsequent studies evaluating OSA and HTN have been inconsistent in their findings. However, when applying stricter criteria such as ambulatory blood pressure monitoring (ABPM) or other overnight BP monitoring with PSG evaluations, the relationship between OSA and BP in children is becoming clearer. Despite the stricter criteria, the data is still inconsistent among the different reports (Table 4). Of the studies using ABPM to measure BP, all except one (Amin et al. 2004) found a significant relationship between OSA and higher BP, primarily sleep BP. In this study, the participants were divided into three groups based on their AHI, and the group with the highest AHI ( $>5$ ) had the lowest diastolic BP during wakefulness. There was no difference in any of the other BP variables including average wake systolic and sleep systolic and diastolic BP. The authors also analyzed BP variability defined as the average standard deviation of wake and sleep systolic, diastolic, and mean arterial BP. With this analysis, there was a dose-dependent increase in variability across the three AHI groups for wake systolic BP, as well as sleep systolic and diastolic BP. The authors proposed that variability in BP during both sleep and wakefulness suggests autonomic instability in children with OSA, resulting in BP dysregulation. The same group of authors later performed a similar, but more rigorous study, and detected significantly elevated BPs (except for sleep systolic BP) in those

with severe OSA compared to controls (Amin et al. 2008). Furthermore, the relative predictive contributions of AHI and BMI were similar for all measures of BP except sleep diastolic BP, where AHI had a significantly greater effect.

In the latter study, an additional ambulatory BP variable was evaluated, the morning surge, defined as the slope of BP from the beginning of the last hour of sleep to the end of the first hour of awakening. In adults, the morning surge has been associated with cardiovascular events such as myocardial infarction and stroke. The children in this study with severe OSA had a morning BP surge significantly higher for systolic, diastolic, and mean arterial BP than the controls. Echocardiographic measures of the left ventricle were also assessed in this study, but had no reported relationship to the morning surge. This remains the only study evaluating the association of the morning surge with OSA in children, so further exploration of its implication in children is needed.

Of the remaining studies using ABPM, all have found a significant relationship between OSA and elevated BP for sleep systolic or diastolic BP. Li et al. defined three OSA groups by AHI with Group 1 as the controls ( $AHI < 1$  and no snoring) and Group 3 with an  $AHI > 5$  (Li et al. 2008). Group 3 had a significantly higher wake and sleep systolic and diastolic BP z-score defined by Wühl et al. (2002) than the other groups but wake systolic BP was no longer significant after controlling for BMI. In another study, Leung et al. only compared two groups ( $AHI < 5$  and  $AHI \geq 5$ ) by BP index defined as the measured BP divided by the 95th percentile for ABP (Leung et al. 2006). They also reported greater systolic and diastolic BP indices in the high AHI group, but the difference in diastolic BP was only for sleep. Weber et al. also compared two groups (PS versus OSA) and found a significant difference in the sleep diastolic BP (Weber et al. 2012). The most recent studies all found a difference in sleep systolic BP (Au et al. 2013; Xu et al. 2013; Kang et al. 2015). One study also found a difference in wake systolic BP (Au et al. 2013), and another study also found a difference in sleep diastolic BP (Xu et al. 2013). Lastly, Kirk et al. only included participants with OSA and

**Table 4** Comparison of blood pressure studies

Source	OSA classification	Method of BP measurement	Method of BP analysis	Systolic BP results	Diastolic BP results	Mean arterial BP results	Nocturnal dip
Amin et al. (2004)	Controls, mild, moderate OSA by AHI	ABPM	BP index and BP variability	No difference	Lower during wake	No difference	Linear trend across OSA groups
Amin et al. (2008)	Controls, mild, moderate OSA by AHI	ABPM	Raw values	Elevated wake	Elevated wake and sleep	Elevated wake and sleep	NR
Li et al. (2008)	Controls, mild, moderate OSA by AHI	ABPM	z-Score	Elevated wake and sleep	Elevated wake and sleep	Elevated wake and sleep	No difference
Leung et al. (2006)	Low vs high AHI	ABPM	BP index	Elevated wake and sleep	Elevated sleep	NR	No difference
Weber et al. (2012)	OSA vs primary snoring	ABPM	Raw values	No difference	Elevated sleep	Elevated sleep	Decreased for DBP and MBP
Au et al. (2013)	Controls, mild, moderate, severe OSA	ABPM	z-Score	Elevated wake and sleep	No difference	NR	No difference
Xu et al. (2013)	OSA vs non-OSA	ABPM	BP index and load	Elevated sleep index and load	Elevated sleep	NR	Decreased SBP and DBP
Kang et al. (2015)	Primary snoring, mild, mod-severe OSA	ABPM	Raw values and BP index	Elevated wake (raw) and sleep (raw and index)	No difference	Elevated wake and sleep	Decreased systolic

Kirk et al. (2010)	Only included cases with OSA	ABPM	Raw values/hypertension vs normotensive	Mean AHI correlated with sleep BP	Mean AHI a/w sleep and wake	NR	NR
Home et al. (2011)	Controls, PS, mild, moderate OSA by AHI	Finger photoplethysmography	Raw values	Varied	Elevated wake and sleep	Elevated wake and sleep	N/A
Kohyama et al. (2003)	Low vs high AHI	Oscillometric during PSG	BP index	Elevated wake and REMS	Elevated wake and REMS	NR	No difference
Marcus et al. (1998)	OSA vs primary snoring	Oscillometric during PSG	BP index	No difference	Elevated wake and sleep	NR	No difference
Enright et al. (2003)	RDI	Mercury manometer	HTN vs normal	HTN associated with RDI	HTN associated with RDI	NR	N/A
Redline et al. (2007)	OSA vs no OSA	Aneroid manometer	Raw values	Elevated	Elevated	NR	N/A
Reade et al. (2004)	OSA vs non-OSA	Manual BP	BP score	Elevated	Elevated	NR	N/A

OSA obstructive sleep apnea, BP blood pressure, NR not reported, HTN hypertension, N/A not applicable, PSG polysomnography, AHI apnea hypopnea index, REMS rapid eye movement sleep, ABPM ambulatory blood pressure monitor, DBP diastolic BP, MBP mean BP, PS primary snorers



found AHI correlated with wake diastolic BP and sleep systolic and diastolic BP (Kirk et al. 2010).

Additional studies measuring sleep BP by other means (intermittent oscillometric devices without the ambulatory component or continuous finger photoplethysmography) also found a significant relationship between OSA and elevated BP. Horne et al. have been the pioneers in using finger photoplethysmography to measure continuous BP during PSG (Horne et al. 2011). They compared primary snorers ( $\text{OAHl} \leq 1$ ), mild OSA ( $1 < \text{OAHl} < 5$ ), and moderate/severe OSA ( $\text{OAHl} > 5$ ) to controls using the finger photoplethysmography and consistently found an elevated diastolic BP for wake and sleep in all three OSA groups. Only primary snorers had an elevated systolic BP for wake and sleep. Two other studies measured overnight BP intermittently and office BP with an oscillometric device. One study demonstrated participants with high AHI ( $\text{AHI} \geq 10$ ) had a significantly increased systolic and diastolic BP index (Kohyama et al. 2003). One of the first studies to investigate the relationship of BP with OSA found children with OSA had significantly higher wake and sleep diastolic BP than those with primary snoring (Marcus et al. 1998). When the groups were combined, both systolic and diastolic BP significantly correlated with the AHI. The remainder of the studies in Table 4 did not measure overnight BP and found varying results.

Although almost all of the studies using PSG and measuring BP during sleep found an association between OSA and elevated BP, only one found a significant difference in the prevalence of HTN defined by a BP  $\geq$  95th percentile according to reference values for casual or ambulatory measurements. In this study, HTN was defined as the mean SBP or DBP values  $>$ 95th percentile for ABP norms (Wühl et al. 2002) and the prevalence of HTN was compared among three groups according to their AHI: primary snorers ( $\text{AHI} < 1$ ), mild OSA ( $\text{AHI} 1\text{--}5$ ), and moderate-to-severe OSA ( $\text{AHI} \geq 5$ ). There was a higher prevalence of systolic nighttime HTN in those with moderate-to-severe OSA compared to those with primary snoring. Another study using ABPM for the evaluation of BP also included clinic BP in their definition of HTN (Xu et al. 2013).

In this study, HTN was defined as a systolic BP load  $>$  25%, and mean ambulatory and clinic systolic BP  $>$  95th percentile. The results of this study did not reveal a difference in the prevalence of HTN when comparing participants with OSA (an  $\text{AHI} > 5$  or an  $\text{OAHl} > 1$ ) to primary snorers. One of the studies used only casual BP measured by mercury manometer and dichotomized BP into HTN or normal (Enright et al. 2003). In their study, the RDI was a significant predictor for systolic and/ or diastolic HTN, but HTN was defined as a BP  $\geq$  90th percentile for age, gender, and height. Two other studies previously mentioned defined HTN by 95th percentile and illustrate the influence of BMI on BP in OSA. Leung et al. estimated HTN prevalence defined as a mean wake, sleep, and/ or total ABP  $\geq$  95th percentile for ABP reference values. The prevalence of HTN was significantly greater in the high AHI group. However, when analyzed as a linear variable, AHI was a significant predictor of HTN only when obesity was included in the model (Leung et al. 2006). Another study that only evaluated casual BP defined HTN as a casual BP  $\geq$  95th percentile for age, gender, and height (Archbold et al. 2012). They found OSA did not have an association with HTN. However, BP was significantly elevated in participants with OSA and positively correlated with BMI and inversely correlated with total sleep time (not included in Table 4).

### **OSA, HTN, and Obesity**

The influence of BMI must be considered when evaluating the relationship between OSA and HTN since obesity is associated with both conditions. In the previous study by Li et al., BMI was found to be a confounding factor for wake systolic BP, i.e., the association was no longer significant when BMI was included in the model (Li et al. 2008). Similarly, in the study by Kang et al., after adjusting for confounders, only nocturnal systolic BP and MAP were significantly correlated with AHI (Kang et al. 2015). Xu et al. also found an association between nocturnal systolic and diastolic BP and obesity (Xu et al. 2013). Another study divided sleep into REM and non-REM sleep, and found a significant association between

the OAHl in non-REM sleep with both daytime and nighttime systolic BP after adjusting for BMI z-score (Au et al. 2013). The other previously mentioned studies that used PSG to determine OSA status found both BMI and OSA variables (i.e., AHI) to have an independent effect on BP. In one of the studies, OSA remained a significant predictor of BP after controlling for BMI, but the effect of BMI on BP was not reported (Redline et al. 2007). One study not previously mentioned specifically addressed the interaction between OSA, BP, and obesity (Reade et al. 2004). After conducting three separate analysis (OSA versus non-OSA; obese versus nonobese; and obese hypertensives versus obese normotensives), the authors found a significantly higher prevalence of HTN and obesity in the OSA group; a higher prevalence of HTN and OSA in the obese group; and a higher prevalence of OSA in the obese hypertensives. Among obese hypertensives, the hypopnea index and BMI were significant independent predictors of systolic and diastolic BP. These studies suggest there is an independent interaction of BP and BMI with OSA. An interaction between BMI and OSA on BP also exists, but the causal relationship of this interaction and the effect on BP is yet to be elucidated.

### Long-Term Follow Up

For the first time, two groups performed long-term follow-up studies on participants to compare baseline and follow-up BP after 4 years. The results of the original studies were previously cited (Horne et al. 2011; Li et al. 2008). The first study was performed by the group using photoplethysmography to measure BP (Vlahandonis et al. 2013). The participants including controls all repeated the same protocol, 4 years later, including PSG with continuous overnight BP monitoring. They were divided into resolved versus unresolved OSA (OAHl  $\geq 1$ , snoring on night of PSG, or parental report of snoring  $\geq 3$  nights per week) and compared to the control group (OAHl  $< 1$  and no snoring). At baseline, BP was significantly elevated for the resolved and unresolved groups compared to controls.

However, at follow up, there was no difference in BP across the three groups. On a post-hoc analysis, there was a significant *decrease* in nocturnal systolic and diastolic BP between baseline and follow up for both the resolved and unresolved OSA groups. Although participants in the unresolved group still met criteria for OSA, they had a reduction in their OAHl. This may indicate that even small improvements in OSA variables can reduce BP. The second study reports on follow up of participants who had a repeat PSG and ABPM (Li et al. 2014). For this study, the participants were grouped according to their baseline OSA severity (OAHl  $< 1$ , OAHl between 1 and 5, and OAHl  $> 5$ ). They were then divided according to their BMI into normal weight and overweight in an effort to decrease the confounding effect of obesity on OSA and BP. In the normal weight group, there was no change in BMI or OAHl at follow up compared to baseline. There was a significant increase in wake systolic and diastolic BP z-score across the OAHl severity groups at follow up. In the overweight group, there was a significant decrease in BMI z-score in the two less severe OSA groups. The only significant BP finding in the overweight group was a decrease in BP z-score at follow up for wake systolic BP in the same OAHl groups that had a decrease in BMI z-score. When the groups were combined for analysis by multiple logistic regression, baseline OAHl was significantly associated with all BP z-scores at follow up (wake and sleep systolic and diastolic BP). Furthermore, the change in OAHl was significantly associated with sleep BP z-scores at follow up. Lastly, baseline BMI z-score and change in BMI z-score were associated with wake and sleep systolic BP z-score. This data demonstrates the complex relationship between OSA, BMI, and BP, and also suggests that OAHl severity at baseline has a significant influence on BP long term, independent of BMI.

### Nocturnal Dipping and OSA

Nocturnal dipping refers to the normal physiologic decline in BP during sleep. Normally, the mean

nocturnal dip is 10–20% lower than the mean daytime BP. Abnormal nocturnal BP patterns can vary from a minimal decline in mean nocturnal BP (< 10% dip) to a rise in nocturnal BP above normal daytime values (reversed dipping) (Urbina et al. 2008). In a study comparing adults with OSA to controls, only patients with OSA were nondippers, even though one of the controls had HTN (Suzuki et al. 1996). After controlling for several variables including age and BMI, only the RDI was a significant predictor of nondipping status. In children, similar to OSA and HTN, the association of nondipping with OSA is not consistent. From the previous studies evaluating 24-hour ABP, most do not show a statistically significant difference in the proportion of nondippers among children with OSA compared to those without OSA. Two of the studies demonstrated a higher proportion of nondippers in the OSA group compared to the group without OSA (29% vs 19% and 12% vs. 4%, respectively), but the difference was not statistically significant (Kohyama et al. 2003, Marcus et al. 1998).

Rather than comparing the proportion of nondippers, other studies have examined the mean nocturnal dip according to OSA, either in multiple groups defined by AHI or according to the presence or absence of OSA. In the first study, the mean nocturnal dip was blunted (<10%) for systolic BP in both groups with an AHI > 1 (Amin et al. 2004). In the second study, there was no difference in the mean nocturnal dip or in the proportion of nondippers per group (Li et al. 2008). Interestingly, in the third study, the mean systolic dipping was significantly decreased in the moderate to severe OSA group (AHI  $\geq$  5) compared to the mild OSA group (1  $\leq$  AHI  $\leq$  5), but the difference was not significant when compared to the controls (Kang et al. 2015). When comparing only two groups, OSA versus no OSA, differences in nocturnal dipping have been detected. One study detected a difference in dipping percentage for diastolic and mean arterial BP as well as a significant difference in the proportion of non-dipping among those with OSA (Weber et al. 2012). Xu et al. reported a significant decrease in systolic and diastolic nocturnal dipping in those with OSA (Xu et al. 2013). The inability to consistently demonstrate significant

differences in the nocturnal dip among OSA groups is likely another result of the heterogeneity among studies, but some studies suggest pubertal status may have an influence (Horne et al. 2011; Westerstahl et al. 2014). Regardless, a child or adolescent undergoing evaluation for elevated BP with a blunted nocturnal dip on ABPM warrants further screening for OSA, especially in the presence of other risk factors or symptoms of OSA. However, the first step when screening further for OSA is to verify the sleep times used for analysis of the ABPM and if the patient slept well while wearing the ABPM.

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### Left Ventricular Geometry in Patients with OSA

Left ventricular hypertrophy (LVH) continues to be the most common surrogate marker of end organ damage in children and adolescents with systemic HTN. Adult data suggests LVH is independently associated with OSA. One study in adults with OSA demonstrated the intermittent obstructive apneas lead to increased afterload (Tkacova et al. 1998) which is thought to contribute to the development of LVH. Therefore, patients with both HTN and OSA may have an even greater risk of LVH. One of the first studies addressing left ventricular geometry and OSA in children reported patients with OSA had a significantly increased left ventricular mass index (LVMI) without a difference in right ventricular dimensions when compared to primary snorers (Amin et al. 2002). The only significant predictor of LVMI was AHI independent of age, gender, and BMI. This dose-dependent effect of the severity of OSA on LVMI was consistent in a later report from the same group with additional participants (Amin et al. 2005). However, a third study from the same group did not detect a significant difference in LVMI with increasing severity of OSA, but there was a difference in left ventricular relative wall thickness (another marker of LV remodeling) between controls and the severe OSA group (Amin et al. 2008). All BP parameters (wake and sleep systolic, diastolic, and mean arterial BP) were significant predictors for this

relationship. Another study evaluating echocardiographic parameters in adolescents with OSA compared to controls did not find a difference in LVMI between the two groups despite a correlation between the RDI and left ventricular posterior wall thickness (Sanchez-Armengol et al. 2003). In the study that only included participants with OSA and measured BP by ABPM, the LVMI was normal for all participants, even for the few detected to have HTN (Kirk et al. 2010). A recent retrospective review of obese children who underwent ABPM, PSG, and echocardiography found an association between LVMI and BMI z-score and no association with any measures of OSA (Westerstahl et al. 2014). Although the evidence for LVH in OSA in children and adolescents is scant, the association is likely to be as complex as the relationship between OSA, obesity, and HTN with the likelihood that all three variables cause changes in LV geometry.

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## Treatment

Adenotonsillectomy is the recommended first-line treatment for OSA in children older than age 2 years (Ehsan and Ishman 2016). Other surgical treatment options are available but are often reserved for those with complex medical histories and/or craniofacial abnormalities. These include uvulopalatoplasty, nasal surgery, tongue reduction surgery, maxillofacial surgery, or in extreme cases with comorbidities, tracheostomy. Recently, hypoglossal nerve stimulators, which increase the tone of the upper airway during sleep, are currently being studied in adults (Strollo et al. 2014). For those who are not surgical candidates or who fail to have a response to surgery, continuous positive airway pressure (CPAP) is a nonsurgical alternative (Ehsan and Ishman 2016). CPAP is fairly well tolerated in children, but compliance is poor secondary to the discomfort of the mask or minor side effects such as rhinorrhea, nasal congestion, or dryness. Alternatively, medical management with a combination of intranasal steroids and leukotriene inhibitors, such as montelukast, has shown promising results to treat mild to moderate OSA in children (Kheirandish-Gozal et al. 2014).

There remain few studies reporting the treatment effect of OSA on BP in children. In the aforementioned case series by Guilleminault et al. five of the eight patients with OSA had HTN at presentation (Guilleminault et al. 1976). Those who underwent adenotonsillectomy demonstrated the improvement of symptoms on follow-up PSG and were no longer hypertensive. Two patients with HTN had extreme cases of OSA and required tracheotomy. Both cases also showed significant improvement in OSA symptoms and resolution of HTN after surgery. Three studies have specifically evaluated the effect of adenotonsillectomy on BP in children. Two studies used only casual BP measurements. In the first study, children with complete resolution of OSA after surgery (AHI < 1) had a significant decrease in diastolic BP but not in systolic BP (Apostolidou et al. 2008). The second study divided the study population into obese and nonobese to evaluate the differences in BP postsurgery between the two groups (Kuo et al. 2015). Regardless of the outcome regarding their OSA severity, the nonobese group had a decrease in diastolic BP index postoperatively. The obese group did not have a change in their BP after adenotonsillectomy, again, demonstrating the interaction between OSA, obesity, and BP. One study using ABPM found that the 24-hour diastolic ABP load was reduced after surgery (Ng et al. 2010). A subgroup analysis of those with HTN prior to surgery demonstrated an improvement in sleep BP loads for both systolic and diastolic BP.

Children with an improvement in the AHI have also shown an improvement in behavioral and cognitive symptoms after treatment of OSA (Shine et al. 2006), and some studies have even shown an improvement in left ventricular geometry and/or function. For example, one of the previously mentioned studies by Amin et al. compared pretreatment and posttreatment left ventricular diastolic function by mitral inflow velocity (Amin et al. 2005). Treatment for OSA either consisted of adenotonsillectomy +/- uvulopalatoplasty, or CPAP. Pretreatment there was a progressive decline in diastolic function across the OSA groups correlating with increasing severity. Posttreatment, regardless of therapy, the

OSA groups had an improvement in diastolic function to a level similar to controls (primary snorers). Another study demonstrated resolution of differences in left ventricular measures and compliance between the OSA and control groups after adenotonsillectomy (Gorur et al. 2001).

## Conclusions

Despite the heterogeneity and conflicting data, there is growing evidence in the literature supporting the association between OSA and elevated BP in children and adolescents. The use of ABPM or other measure of BP during sleep is imperative when evaluating a child or adolescent for hypertension to identify an additional risk factor for OSA and associated complications. The evaluation should include clinical signs and symptoms of OSA during the history and physical exam. Adenotonsillar hypertrophy and obesity are the two most common risk factors for OSA in children. The presence of either in conjunction with HTN, particularly elevated nighttime BP, deserves further evaluation for OSA. Although the association between OSA and HTN has been established independent of obesity, obesity also has an independent association each with OSA and with HTN. How the three conditions interact and whether there is a causal relationship among the conditions is still not clear and warrants further investigation. Furthermore, changes in left ventricular structure in children are associated with both HTN and OSA, and after treatment of OSA alone, measures of LV geometry improve. Therefore, further research in OSA and HTN is essential as this would contribute to a more targeted and informed evaluation and treatment in children and adolescents with HTN in regard to OSA.

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# Hypertension in the Pregnant Teenager

32

Tracy E. Hunley, Neerav Desai, and Deborah P. Jones

## Abstract

Hypertension occurs in approximately 10–20% of pregnancies and is associated with significant maternal and fetal morbidity. Most importantly, it results in preterm delivery and is associated with other conditions in the spectrum of placental ischemic disease such as intrauterine growth retardation and placental abruption. Chronic hypertension increases the risk for gestational hypertension and preeclampsia. Hypertension during pregnancy is also associated with increased future cardiovascular risk in the mother and her offspring. Topics to be discussed in this chapter include the classification of hypertensive disorders in pregnancy, normal blood pressure patterns during pregnancy, the pathophysiology of gestational hypertension and preeclampsia, features unique to the pregnant adolescent, the epidemiology and outcome of hypertension during pregnancy, and treatment guidelines.

## Keywords

Gestational hypertension • Preeclampsia • ABPM • Preterm birth • Adolescence • Placental ischemia

## Abbreviations

2-ME	2-Methoxyestradiol
ABPM	Ambulatory Blood Pressure Monitoring
ACEi	Angiotensin Converting Enzyme inhibitors
ARB	Angiotensin Receptor Blockers
ANP	Atrial Natriuretic Protein
BP	Blood Pressure
BMI	Body Mass Index
COMT	Catechol- <i>O</i> -Methyl Transferase
CI	Confidence Interval
SBP	Systolic BP
DBP	Diastolic BP
sEng	Endoglin
GFR	Glomerular Filtration Rate
HELLP	Hemolysis, Elevated Liver Enzymes, Low Platelets syndrome
HIF	Hypoxia Inducible Factor-1
MAP	Mean Arterial Pressure
OR	Odds Ratio
PIGF	Placental Growth Factor
sFlt1	Soluble Fms-Like Tyrosine Kinase 1
VEGF	Vascular Endothelial Growth Factor

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## Introduction

Hypertension occurs in approximately 10–20% of pregnancies and is associated with significant maternal and fetal morbidity. Most importantly, it results in preterm delivery and is associated with other conditions in the spectrum of placental ischemic disease such as intrauterine growth retardation and placental abruption (Roberts et al. 2013; Lindheimer et al. 2010). Both chronic hypertension and obesity increase the risk for worsening hypertension during pregnancy (including preeclampsia) as well as preterm birth and fetal growth insufficiency. Blood pressure (BP) levels during the first half of pregnancy are lower than before pregnancy, a physiologic change that challenges the clinician in the choice of BP thresholds at which to initiate or to achieve with antihypertensive therapy.

Hypertension during pregnancy is associated with increased future cardiovascular risk in the mother and her offspring as can be viewed as a stress test for future cardiovascular risk. Topics to be discussed in this chapter include the care of the pregnant adolescent with hypertension, classification of hypertensive disorders in pregnancy, normal BP patterns during pregnancy, the pathophysiology of preeclampsia, features unique to the pregnant adolescent, the epidemiology and outcome of hypertension during pregnancy, and treatment guidelines. There are very few studies which focus on the adolescent with hypertension, and, therefore, most of the references cited in this chapter relate to hypertension during pregnancy in general. If available, studies which specifically address the pregnant teenager will be discussed.

## Case

A 16-year-old female was followed in the pediatric nephrology clinic since the age of 9 years for hypertension secondary to renal scarring and vesicoureteral reflux. She was treated with valsartan 160 mg daily and amlodipine 5 mg daily. Past medical history was remarkable for imperforate anus, s/p repair as an infant, linear growth delay, delayed puberty, and recurrent urinary tract infections. Her electrolytes were normal and serum creatinine 0.7 mg/dl. Her urine protein excretion was abnormal, with a baseline urine protein/creatinine ratio of 0.5 mg/mg (normal, <0.2 mg/mg). Her follow-up to clinic was sporadic, as she missed about 50% of scheduled appointments. Her mother called to report that she was pregnant and requested advice on continuation of her antihypertensive medications. She was advised to discontinue valsartan and was scheduled to see an obstetrician.

This case illustrates several questions which arise in the pregnant adolescent with preexisting hypertension: How is preeclampsia detected in the setting of baseline proteinuria and hypertension? What is the risk to the patient and to her baby? What is the goal for BP levels? Which medications should be used to control BP? Should the

pregnancy be terminated due to conception while on valsartan?

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## The Pregnant Adolescent: General Considerations

Adolescent pregnancy is a significant burden across the world, with an estimated 16 million children born to women between 15 and 19 years of age ([www.guttmacher.org](http://www.guttmacher.org) 2012). The USA has one of the highest rates among developed countries; however, this number has been steadily decreasing between 1990 and 2010. It is estimated that up to two thirds of adolescent pregnancies in the USA are unplanned (Finer and Henshaw 2006). Approximately two thirds of teenage pregnancies result in live birth and one third end in abortion (Kost and Heushaw 2014). There is considerable variation among regions of the USA, with southern states having the highest teen pregnancy rates. There is also significant variation between races, with African American and Hispanic adolescents becoming pregnant at twice the rate of non-Hispanic white teens in the USA. Finally, lower socioeconomic status and lower levels of parental education also have strong correlations with teenage pregnancy (Hamilton et al. 2011). These statistics emphasize that providers who are dealing with this age group, even on an infrequent basis, will most likely encounter teenage pregnancy in various clinical settings.

There are several features about adolescent pregnancy which cause it to be classified as high risk. Pregnant teenagers have a higher incidence of domestic violence, sexual abuse, sexually transmitted infections, substance use, and nutritional imbalance (Quinlivan and Evans 2005; Lenders et al. 2000; Black et al. 2012). Many comprehensive high risk centers incorporate a multidisciplinary team of providers which can include a social worker, counselor, nutritionist, obstetrician, and adolescent medicine provider. This team can address the multiple factors that will improve outcomes for mothers and infants (Quinlivan and Evans 2004).

Unplanned pregnancy can be viewed as a disruption of the psychosocial development of a

teenager. Physical development along with full reproductive potential is usually completed by early and middle adolescence, between the ages of 12 and 16. Emotional and social maturity typically occurs in later adolescence, between the ages of 17 and 20 (Brown and Brown 2006). This incongruous development results in many teen mothers and fathers who are emotionally unprepared to handle a pregnancy and the responsibilities associated with it. Teens are suddenly forced to reckon with the many burdens of prenatal and postpartum care, which include infant care-taking responsibilities, personal health and nutrition, finances, and educational or vocational responsibilities (Paranjothy et al. 2009). Adolescent women who have concurrent chronic medical conditions, such as hypertension or diabetes, face the additional challenge of maintaining optimal control of their health to avoid adverse effects to the child (Sibai 1991). All of these extra tasks of pregnancy and parenting represent a major emotional conflict for teenage women who are still attempting to establish their own identity.

Teen mothers also face many barriers to high quality preconception and prenatal care. These obstacles include social stigma, transportation issues, confidentiality, financial burden, and lack of information about preconception care. Confidentiality is perhaps the most important of these barriers. Teens are less likely to seek contraceptive or prenatal care due to concerns about confidentiality among family and peers. This is demonstrated by the fact that adolescent females wait an average of 1 year to seek contraceptive counseling after initiating sexual intercourse because they are afraid of their parent finding out (2012). As a result, most teenage pregnancies occur within the first year of becoming sexually active. Most states protect the rights of minors to seek contraception counseling and prenatal care; however, many states still restrict a minor's right to termination of pregnancy without parental consent (2012).

Pregnant adolescents require additional resources and specialized care, so clinicians can utilize existing relationships amongst the teen and her family, peers, and partners. The initial preference for the teenager may be to conceal the

pregnancy from family members or her partner due to fear of negative consequences. Providers are encouraged to engage a close family member such as a parent or an older sibling during the initial office visit when the pregnancy is confirmed. Family members can provide the teen mother with much-needed support in the tenuous days and weeks ahead when decisions will have to be made about choice of pregnancy outcome and access to prenatal care.

### Definitions of Hypertensive Disorders of Pregnancy

Interpretation of epidemiologic studies and outcomes research in the area of gestational hypertension and preeclampsia has been challenged by a lack of agreement on terminology (Lindheimer et al. 2010). Such definitions may differ depending upon the working group from which they originate. Furthermore, the correct categorization may not be clear until postpartum. Diagnostic criteria are designed to be rather loose or highly sensitive, so as to detect all possibly affected individuals early in the course with the goal that maternal and infant morbidity/mortality can be minimized. The following classification of hypertensive disorders in pregnancy was adopted by the International Society for the Study of Hypertension in Pregnancy (ISSHP) (2013): preeclampsia, chronic hypertension, preeclampsia superimposed upon chronic hypertension, and gestational hypertension (Table 1). The term pregnancy-induced hypertension which is not

included in the classification scheme shown above has been used in some studies and publications; use of this term is discouraged because it might refer to either gestational hypertension or preeclampsia.

Chronic hypertension is defined as SBP  $\geq 140$  and/or DBP  $\geq 90$  before pregnancy or before 20 weeks gestation. It is possible that chronic hypertension may be initially designated as gestational hypertension with delay in the final diagnosis until 12 weeks postpartum because hypertension that is diagnosed during pregnancy but that does not resolve postpartum is considered chronic. Preeclampsia is a pregnancy-specific syndrome which usually occurs after 20 weeks gestation; it includes gestational BP elevation (same parameters as above) and proteinuria. In the absence of proteinuria, additional symptoms such as headache, blurred vision, abdominal pain, thrombocytopenia, and elevation of hepatic transaminases also indicate the presence of preeclampsia.

During uncomplicated pregnancy, the urine protein excretion increases to 200–260 mg/24 h with urinary microalbumin excretion levels up to 29 mg/24 h. Proteinuria is defined as  $\geq 300$  mg per 24 h, by urine protein/creatinine ratio (Upc)  $> 0.3$  or if those methods are not available, then  $\geq 1+$  by dipstick on at least two random urine samples collected more than 6 h apart (Dekker 2011). There are concerns about use of Upc in place of a timed urine collection. The correlation between 24 h urine protein and Upc was only moderate ( $R^2 = 0.41$ ) and a Upc  $< 0.3$  had a negative predictive value of 47.5% among women with suspected preeclampsia (Durnwald

**Table 1** Classification of hypertensive disorders of pregnancy (Adapted from Garovic 2012)

<20 gestational weeks	$\geq 20$ gestational weeks	$\geq 12$ weeks postpartum	Diagnosis
Normotensive	Gestational HTN + proteinuria	Resolution of HTN and proteinuria	Preeclampsia
Normotensive	Gestational HTN – no proteinuria	Resolution of HTN	Gestational HTN
Normotensive	Gestational HTN – no proteinuria	Persistent HTN	Chronic (incident) HTN
Chronic (prevalent) HTN	+proteinuria	Resolution of proteinuria	Preeclampsia superimposed upon chronic HTN
Chronic (prevalent) HTN	–proteinuria	Persistent HTN	Chronic HTN

and Mercer 2003). Indeed, while classically, proteinuria has been considered a criterion for preeclampsia, not all women with preeclampsia have proteinuria. More recent definitions allow for inclusion of those individuals without proteinuria to be considered to have preeclampsia if they have evidence for other organ dysfunction, (thrombocytopenia, liver dysfunction, renal dysfunction, CNS symptoms). Eclampsia is defined as seizures without other causes in someone with preeclampsia. Edema has been omitted as a criterion.

Preeclampsia may also occur in the individual with chronic hypertension and may be difficult to distinguish from worsening chronic hypertension. In females such as the illustrative case with hypertension secondary to renal parenchymal disease, detection of preeclampsia may be challenged by preconception proteinuria. Furthermore, chronic hypertension is a significant risk factor for the development of preeclampsia. The onset of proteinuria or marked worsening of proteinuria in the setting or worsening hypertension and development of thrombocytopenia or hepatic transaminase elevation increase the likelihood that preeclampsia is superimposed upon chronic hypertension as opposed to worsening chronic hypertension.

Gestational hypertension describes the scenario of detection of hypertension in a pregnant female without known chronic hypertension or signs of preeclampsia, with the understanding that she may go on to develop preeclampsia or have chronic hypertension postpartum. If BP is normal by 12 weeks postpartum, then chronic hypertension can be excluded. Hypertension during pregnancy can be due to a preexisting condition (chronic hypertension – primary or secondary – most often related to underlying renal disease) or pregnancy-induced hypertension.

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### **BP Patterns Through the Course of Pregnancy**

Physiological changes during pregnancy include upregulation of the renin-angiotensin-aldosterone system and global vasodilation, resulting in increased glomerular filtration rate and renal

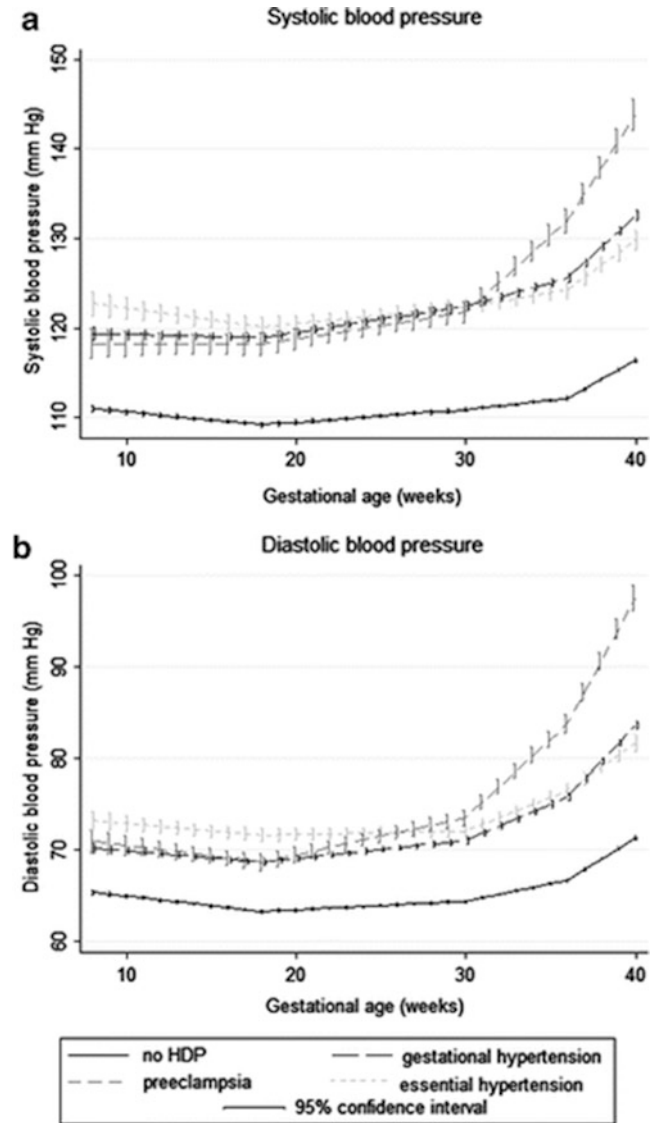
plasma flow. In addition, there may be increased renal volume (Berry and Atta 2016). During pregnancy, BP typically decreases during the first trimester and early second trimester [first 20 weeks] and then increases in the late second trimester and third trimesters to values similar to those at the beginning of gestation (Lindheimer et al. 2010). Clinic BP patterns were examined during gestation in more than 13,000 women from the Avon Longitudinal Study, 4% of whom were younger than 20 years of age (Macdonald-Wallis et al. 2012). Eighty-percent were normotensive; gestational hypertension developed in 14.6%, preeclampsia in 2.1%, and 3.3% had primary (or chronic) hypertension. BP levels were higher by 8 weeks gestation in women who developed gestational hypertension or preeclampsia (Fig. 1). Baseline BP levels were similar between women who developed gestational hypertension and preeclampsia despite the assumption of divergent etiologies/mechanisms. Those individuals who developed preeclampsia failed to demonstrate the typical decline in BP during the first half of gestation and were characterized by a sharper slope of increase in BP during the second half of gestation (Fig. 1). Those with chronic hypertension had higher BP levels during early gestation but did have a mid-gestational decline in BP, in a fashion similar to normal women. The magnitude of the increase in BP in the second half of gestation was also associated with earlier delivery.

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### **Ambulatory Blood Pressure During Pregnancy**

Several studies have measured ambulatory BP in midtrimester in nulliparous females with normal baseline BP and have examined differences in and magnitude of ambulatory BP levels in predicting preeclampsia and pregnancy-induced hypertension (Kyle et al. 1993; Higgins et al. 1997). There were significant differences in both clinic and ambulatory systolic BP (SBP) between the normal and preeclamptic groups at 18 weeks gestation; those who went on to develop preeclampsia had a mean ambulatory SBP 4.7 mmHg greater than those who did not.

**Fig. 1** Average trajectories of systolic and diastolic blood pressures by hypertensive disorders of pregnancy in the unadjusted joint model ( $N = 13,016$ ) (From Macdonald-Wallis et al. (2012))

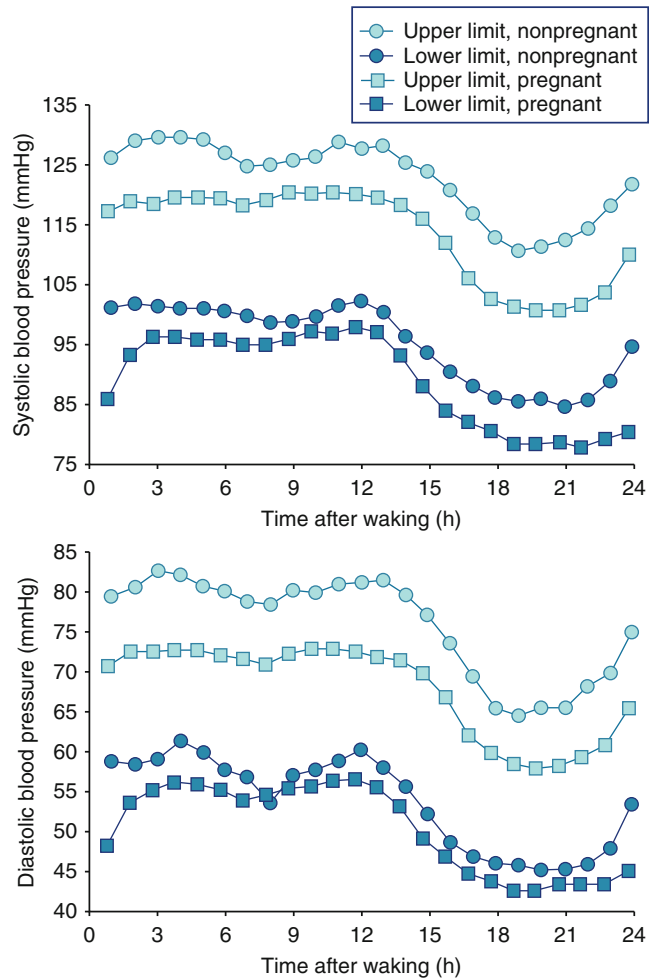


At 28 weeks, there were significant differences in ambulatory systolic and diastolic BP; those who went on to develop preeclampsia had a mean ambulatory SBP 6.9 mmHg and DBP 4.4 mmHg greater than those who did not. Diurnal pattern was maintained; those in the highest quartile of BP had the highest incidence of preeclampsia (Kyle et al. 1993). Positive predictive values using the 95th percentile cutoff for daytime, nighttime, and 24-h BP levels were poor.

Differences in diurnal variation were observed in a larger study; this study (in contrast to the previous)

distinguished between two outcomes—gestational hypertension and preeclampsia (gestational hypertension + proteinuria) and compared them to a normal group. The group with preeclampsia had significantly higher nighttime BP, with a much smaller nocturnal decline, in contrast to the gestational hypertension group, which had higher daytime and nighttime BP as compared to the normal group but maintained a normal ratio between day/night mean BP. Despite significantly different mean BP levels in both hypertensive groups as compared to the normal group, ambulatory BP

**Fig. 2** Circadian 90% tolerance intervals for systolic and diastolic blood pressure. From a reference population of normotensive nonpregnant and normotensive pregnant women who were assessed by 48 h ambulatory monitoring in the second trimester of pregnancy (From Hermida and Ayala (2004))



levels performed poorly in predicting who would develop gestational hypertension or preeclampsia (Higgins et al. 1997).

The pattern of ambulatory BP throughout pregnancy has been extensively characterized by Ramón Hermida and coworkers, who have argued that use of clinic BP levels with the threshold of 140/90 underestimates the incidence of gestational hypertension. Furthermore, they have offered several methods to define hypertension during pregnancy. Similar to other clinical situations, they argue that clinic BP levels misclassify individuals at risk. Pregnant women with masked gestational hypertension (high ambulatory and normal clinic BP) have comparable outcomes [preterm delivery and IUGR] as those with both abnormal ambulatory and clinic BP (Hermida and

Ayala 2002). Differences in mean 24 h BP levels were noted toward the end of the first trimester; those who developed gestational HTN had a mean 24 hr ambulatory BP of 115/67 as compared to normotensive women, whose mean 24 hr ambulatory BP was 103/60. As illustrated in Fig. 2, ambulatory BP 90th percentile threshold levels are lower in the normal pregnant female as compared to the normal nonpregnant female.

Evidence continues to accumulate that reliance on office BP may underdiagnose hypertension during pregnancy. ABPM was performed in 87 women with high-risk pregnancy in whom office BP was considered normal (<140/90). Thirty-three percent had masked hypertension. Those with nocturnal hypertension had 4.7 times greater risk for preeclampsia/eclampsia (Salazar

et al. 2016; Bilo and Parati 2016). Although the supporting evidence was rated as low, the most recent ACOG report recommended ABPM for pregnant women with suspected white coat hypertension to provide a more accurate representation of BP (2013).

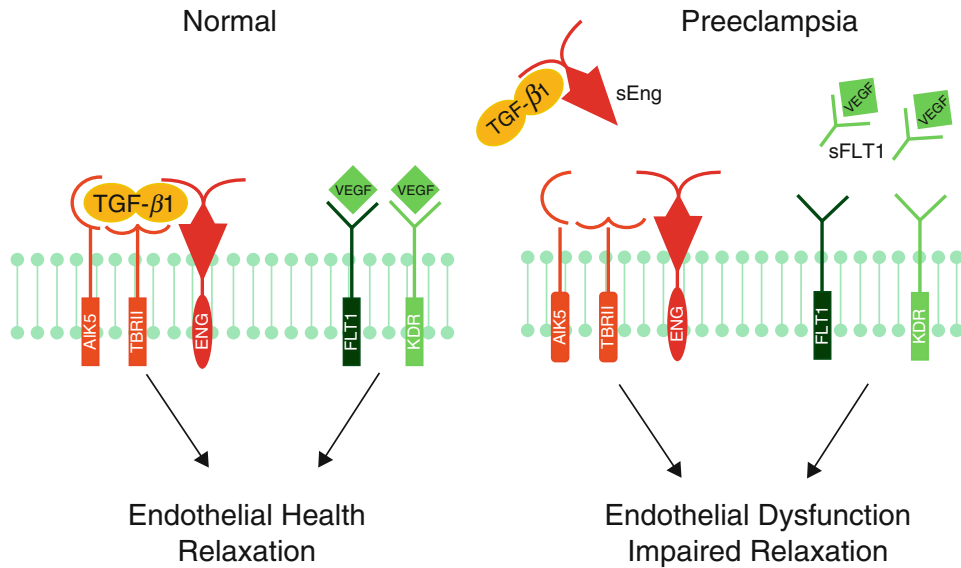
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## Mechanisms of Gestational Hypertension and Preeclampsia

Preeclampsia, the most severe form of gestational hypertension, resolves with delivery. The occurrence of preeclampsia with molar pregnancies as well, however, points to the crucial role of the placenta, as opposed to the fetus, in its pathophysiology. During normal placentation, embryonic cytotrophoblast cells migrate into the uterine spiral arteries leading to their remodeling into high capacitance, low resistance vascular channels which provide for adequate placental and fetal perfusion (Powe et al. 2011). In so doing, cytotrophoblast cells acquire an endothelial phenotype, and spiral artery remodeling extends through the most superficial uterine layer, the decidua, and into the myometrium. These processes are attenuated in the preeclamptic placenta, in which myometrial-level arterial remodeling was seen in only 27% of arteries in one study (range, 3–41%), compared to 88% for placentae from non-preeclamptic pregnancies (range, 76–100%) (Brosens et al. 2011). Inadequate spiral artery remodeling in preeclampsia leads to reduced placental perfusion. Indeed, Doppler assessment of maternal uterine arterial blood flow demonstrates alterations reflecting this inadequate conversion of spiral arteries. Thus, among >4000 singleton pregnancies, odds ratios for gestational hypertension, preeclampsia, and early-onset preeclampsia were 1.5 [95% CI 1.02–2.26], 2.1 [1.28–3.36], and 4.47 [1.50–13.35], respectively, in the presence of diastolic notching in bilateral uterine arteries (heralding reduced perfusion) showed (Espinoza et al. 2010). The higher occurrence of preeclampsia in patients with preexisting hypertension, renal disease, obesity, and diabetes may relate to preexisting vascular abnormalities which render the spiral arteries resistant to cytotrophoblast cell invasion and remodeling.

The mechanisms and importance of uterine spiral artery remodeling to normal pregnancy have recently been further elucidated to include a prominent role for locally produced (uterine) atrial natriuretic protein (ANP) and the enzyme corin, which converts pro-ANP to ANP. ANP stimulates trophoblast invasion and both ANP and corin null mutant mice, when pregnant, demonstrate impaired trophoblast invasion/spiral artery remodeling as well as hypertension, proteinuria, and renal pathology. Human uterine samples from preeclamptic patients showed corin deficiency and pre-ANP excess compared to unaffected pregnancies (Cui et al. 2012). In a study of nearly 500 blood samples from 122 women throughout gestation, preterm preeclamptic mothers had lower circulating corin levels than those without preeclampsia and higher circulating pro ANP levels (Khalil et al. 2015). Further, two human corin gene mutations have been identified in preeclamptic Chinese women which markedly reduced ANP generation (Cui et al. 2012). More recently, two more common single nucleotide polymorphisms in the human CORIN gene (in almost perfect linkage disequilibrium) were found to be significantly associated with preeclampsia in Caucasians as well (Stepanian et al. 2014).

A poorly perfused, hypoxic placenta is thought to be central to the development of preeclampsia. Reduction in uteroplacental perfusion in a variety of mammals, including primates, has been shown to cause maternal hypertension (Gilbert et al. 2008; Makris et al. 2007). In a well-characterized rat model, 40% reduction in uteroplacental perfusion on day 14 of a 21-day gestation induces dramatic maternal cardiovascular changes. On gestation day 19, animals displayed increased mean arterial pressure (MAP), increased total peripheral resistance, decreased renal blood flow and GFR, proteinuria, and endothelial dysfunction. Ex vivo investigation of vascular strips from similarly treated animals showed decreased relaxation in response to acetylcholine and decreased nitric oxide generation. Thus, reduced uteroplacental perfusion appears to tip the maternal cardiovascular balance towards vasoconstriction (Gouloupoulou and Davidge 2015).



**Fig. 3** Soluble fms-like tyrosine kinase 1 (*sFlt1*) and soluble endoglin (*sEng*) cause endothelial dysfunction by antagonizing vascular endothelial growth factor and transforming growth factor- $\beta$ 1 (*TGF- $\beta$ 1*) signaling. VEGF and TGF- $\beta$ 1 maintain endothelial health. During normal pregnancy, vascular homeostasis is maintained by physiological levels of VEGF and TGF- $\beta$ 1 signaling in the

vasculature; however, in preeclampsia, excess placental secretion of sFlt1 and sEng, which are endogenous antiangiogenic protein, inhibits VEGF and TGF- $\beta$ 1 signaling in the vasculature, resulting in endothelial dysfunction and the accompanying decreased prostacyclin and nitric oxide production as well as release of procoagulant proteins. TBRII indicates TGF- $\beta$ 1 receptor (From Powe et al. (2011))

Conversely, renal venous occlusion caused by compression of the left renal vein by the gravid uterus has been proposed as an overlooked contributor to gestational hypertension and preeclampsia. The resultant higher renal interstitial pressure reduces the arterial flow and activates the RAAS as well as the sympathetic nervous system leading to systemic hypertension. Persistence of increased renal interstitial pressure results in ischemia leading to release of endothelin and other vasoactive mediators (Reuter et al. 2016).

Placenta-derived circulating factors have been identified which link abnormal placentation and the aberrations seen in maternal physiology with preeclampsia. Gene expression profiling of placental tissue from women with and without preeclampsia identified upregulation of soluble fms-like tyrosine kinase 1 (sFlt1) and elevated circulating sFlt1 in those with preeclampsia. As a splice variant of a vascular endothelial growth factor (VEGF) receptor lacking cytosolic and transmembrane domains, sFlt1 is circulating yet still able to bind VEGF, though without

downstream effects, and thus acts to inactivate VEGF and placental growth factor (PlGF) as well. Normally, VEGF is a proangiogenic factor which promotes the proliferation and survival of endothelial cells. VEGF fosters vasodilation through interaction with the endothelial KDR receptor which upregulates endothelial nitric oxide synthetase (eNOS) and also maintains endothelial fenestration and vascular permeability (He et al. 1999; Facemire et al. 2009), while the VEGF Flt1 receptor also contributes to endothelial permeability and survival (Takahashi et al. 2004). With 53% homology to VEGF, PlGF potentiates VEGF endothelial maintenance (Powe et al. 2011). Deprived of normal VEGF signal through increasing circulating sFlt1, maternal endothelium becomes dysfunctional (Fig. 3). This includes the renal circulation, where podocyte to endothelial VEGF signaling is essential to maintenance of normal glomerular capillaries, so that diminished VEGF leads to endothelial cell swelling, loss of the intact filtration barrier, and proteinuria. Infusion of sFlt1



(acting as a VEGF trap) into animals (pregnant or not) induced hypertension, proteinuria, and recapitulated the renal findings of severe preeclampsia, including glomerular endothelial cell swelling and intracapillary fibrin deposition. This is similar to observations of hypertension and proteinuria with pharmacologic inhibition of VEGF for cancer therapy (Patel et al. 2008). Because sFlt1 also binds placental growth factor (PlGF), reduced free VEGF and free PlGF levels have been found in preeclamptic women, and these levels were even lower with worsening severity of preeclampsia (Maynard et al. 2003).

In a larger cohort of 120 pairs of nulliparous women with and without preeclampsia, non-preeclamptic women showed an increase in sFlt1 in the last few weeks of gestation which was dramatically surpassed (two to threefold higher) in those with preeclampsia (Levine et al. 2004). Lower PlGF levels were seen (8–45% control level in the last trimester) though depletion of circulating VEGF was harder to demonstrate in this larger cohort in part because of lower VEGF levels in all women (5–10 pg/ml) compared to PlGF levels (50–1000 pg/ml); circulating VEGF represents a small fraction, as the majority of VEGF is membrane bound. Further implicating sFlt1 in the pathophysiology of preeclampsia are observations that its placental expression and maternal circulating level are augmented by hypoxia/hypoperfusion (Hornig et al. 2000; Makris et al. 2007). Lastly, apheresis with a dextran sulfate cellulose column reduced circulating sFlt1 level in severe preterm preeclamptic women and was accompanied by reduction in BP and proteinuria as well as prolongation of pregnancy (Thadhani et al. 2011). This initial whole blood apheresis strategy has recently been improved upon (decreasing procedure-associated hypotension) by first separating out plasma before passing it through a plasma-specific dextran sulfate (PSDS) column (Thadhani et al. 2016). Among women with very preterm preeclampsia (23–32 weeks gestation), lowering sFlt1 through PSDS apheresis allowed continuation of pregnancy for 8 days (range 2–11) and 15 days (range 11–21) after single and multiple treatments, respectively, compared

to 3 days prolongation of pregnancy in untreated contemporaneous controls.

Similarly, excess placenta-derived soluble endoglin (sEng) circulating at higher than normal levels in the preeclamptic mother causes important endothelial effects. This is because membrane bound endoglin is a necessary coreceptor for endothelial TGF beta signaling. In addition to its recognized function to promote cellular proliferation and differentiation, TGF beta is also crucial to normal vascular functioning including vasodilatation through nitric oxide (Venkatesha et al. 2006). As with sFlt1 and VEGF, sEng acts as a ligand trap for TGF beta, lessening its endothelial receptor binding and downstream eNOS signaling and vascular relaxation (Venkatesha et al. 2006). In preeclamptic mothers, reduction in circulating nitrite (metabolic by product of nitric oxide metabolism) correlated with elevations in sEng (as well as sFlt1) (Sandrim et al. 2008).

Effects of sEng and sFlt1 appear synergistic. Thus, while experimental infusion of sFlt1 causes hypertension and proteinuria, coinfusion of sFlt1 and sEng together causes more severe hypertension and proteinuria as well as hemolysis, thrombocytopenia, and elevated hepatic transaminases, recapitulating the HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) (Venkatesha et al. 2006). In assessing for risk of preeclampsia, elevation in either sFlt1 or sEng alone was associated with adjusted odds ratio (OR) of 1.5–2.3 (95% CI 0.4–8.7). Elevation in both produced an OR for term preeclampsia of 31.6 (95% CI 10.7–93.4) (Levine et al. 2006).

Measurements of maternal levels of circulating anti- and proangiogenic factors are being used to improve the diagnostic accuracy of current clinical signs and symptoms of preeclampsia. In a large, urban American obstetric practice, patients with a ratio of PlGF/sFlt1 less than 0.05 multiples of the median (MoM) (a low level of pro-/anti-angiogenic factors) had a dramatically increased risk for preterm delivery (<34 weeks) due to preeclampsia (adjusted odds ratio 7.4). Among those presenting at less than 34 weeks gestation, the addition of the PlGF/sFlt1 ratio to standard clinical tests improved the sensitivity of detecting those at risk of delivery in less than 2 weeks.

Thus, for PIGF/sFlt1 ratios of  $\leq 0.035$  MoM, 0.036–0.34 MoM, and  $\geq 0.35$  MoM the rates of preterm delivery <34 weeks gestation were 94%, 27%, and 7%, respectively (Chaiworapongsa et al. 2014). A multicenter prospective European trial produced similar results in that a low ratio of sFlt1/PIGF (anti-/proangiogenic factors) was able effectively to rule out preeclampsia. A sFlt1/PIGF ratio <38 had a negative predictive power (no preeclampsia in the following week) of 99.3% (99% CI 97.9–99.9) (Zeisler et al. 2016). Such results should allow more precise stratification of preeclampsia risk so that resources can be directed towards those most clearly affected.

Increased expression of sFlt1 is mediated at least in part by hypoxia inducible factor-1 (HIF), credibly linking placental hypoperfusion and findings of increased circulating sFlt1 in preeclampsia (Nevo et al. 2006). 2-Methoxyestradiol (2-ME), which is elevated in normal pregnancies, suppresses HIF. The enzyme responsible for production of 2-ME, catechol-*O*-methyltransferase (COMT), is reduced in the placentas of women with preeclampsia (Barnea et al. 1988). COMT null mutant mice, absent 2-ME, have elevated HIF and sFlt1 and preeclampsia, all ameliorated by exogenous 2-ME administration (Kanasaki et al. 2008). Interestingly, genetic variants associated with lower COMT levels have been associated with recurrent preeclampsia raising the possibility that 2-ME administration might have therapeutic potential for treatment of preeclampsia (Roten et al. 2011; Hernandez et al. 2013).

Vasoconstrictor responses of maternal vasculature are potentiated by increased angiotensin type I receptor signaling. Autoantibodies to the angiotensin AT1 receptor (AT1-AA) have been detected in the serum of preeclamptic women which function as receptor agonists. Increased receptor activity might explain the exaggerated pressor response to angiotensin II observed in preeclamptic compared with normal pregnancies (Wallukat et al. 1999). Various AT1-mediated effects have been demonstrated for these autoantibodies including vasoconstriction, stimulation of plasminogen activator inhibitor-1 (PAI-1) from mesangial cells, and tissue factor expression by vascular cells – all

potentially relevant to maternal cardiovascular and renal changes observed in preeclampsia (Dechend et al. 2003). Importantly, AT1-AA recovered from patients with preeclampsia produced preeclampsia when administered to pregnant mice (Zhou et al. 2008). Underscoring the levels of complexity of preeclampsia causation are observations that AT1-AA leads to increased sEng, as well as the potent vasoconstrictor endothelin-1 (Zhou et al. 2010, 2011). Moreover, recombinant VEGF administration ameliorates experimental AT1-AA mediated preeclampsia, suggesting VEGF blockade by sFlt1 to be an important post AT1 receptor mediator of preeclampsia as well (Siddiqui et al. 2011).

Emerging evidence points to a role for complement dysregulation in preeclampsia and gestational hypertension as well. Placental trophoblasts express three membrane bound complement regulatory proteins: membrane cofactor protein (MCP, CD46), decay accelerating factor (DAF, CD55), and MAC inhibitory protein (MAC-IP, CD59), an inhibitor of terminal complement (Regal et al. 2015). These function to quell the complement activation of normal pregnancy and maintain the health and integrity of the fetal placental unit. In preeclamptic Chinese women, the terminal complement product C5b-9 was elevated in plasma together with C3a and C5a (complement metabolites indicative of activation). As the terminal product of the complement cascade, elevated C5b-9, the soluble membrane attack complex (sMAC), indicates unrestrained complement activation (He et al. 2016). Renal autopsy tissue from women with preeclampsia showed a dramatic increase in glomerular staining for C4d compared to normal pregnancy and chronic hypertensive controls as well as a moderate increase in C1q (Penning et al. 2015). To further investigate these observations, this group used a murine model of preeclampsia induced by injection of exogenous sFlt-1 during pregnancy. These mice subsequently showed marked increase in renal C4d as well. Given the model of preeclampsia induction, these data indicate a link of complement activation to the antiangiogenic state of preeclampsia (increased sFlt-1). Similar results have been found in women with severe

preeclampsia, in whom elevated urine C5b-9 correlated significantly with urine sFlt-1 ( $r = 0.77$ ;  $p < 0.0001$ ) as well as the overall antiangiogenic state of marked elevation in sFlt-1 and suppression of PlGF and VEGF in plasma (Guseh et al. 2015). Sera from patients with severe preeclampsia and HELLP syndrome indicated complement activation which could be blocked in vitro by the anti-C5 monoclonal antibody, eculizumab (Vaught et al. 2016). Indeed, eculizumab has been used to treat severe HELLP syndrome at 26-weeks gestation, resulting in improvement in liver function studies, LDH, haptoglobin, and platelet count, allowing pregnancy to be prolonged by 17 additional days (Burwick and Feinberg 2013).

The pathophysiology of gestational hypertension shares many components with preeclampsia. A significant elevation in the ratio of sFlt1:PlGF in women with gestational hypertension has been observed, though elevation was relatively smaller than the marked elevation in preterm and term preeclampsia (Levine et al. 2004). In the same group of patients, however, sEng was elevated to the same degree as those with preeclampsia, leading the authors to consider/recommend gestational hypertension as a milder form of preeclampsia. In another study, sFlt1 and sEng were both intermediate in patients with gestational hypertension (23.5, 23.6 pg/ml) compared to normal pregnant controls (16.5, 15.5 pg/ml) and preeclamptic women (74.7, 69.2 pg/ml) (Salahuddin et al. 2007). Since the advent of normative data for

sFlt1 and sEng levels in pregnancy, it has been shown that circulating levels above the 95th percentile were seen in 67% and 67% of women with gestational hypertension as opposed to 94% and 89% of women with standard preeclampsia (Hirashima et al. 2011). Women with gestational hypertension demonstrate a reduction in circulating nitrite (reflecting reduced endothelial nitric oxide) though to a lesser degree than preeclampsia (Salahuddin et al. 2007). Similarly, glomerular endotheliosis on renal biopsy (once considered pathognomonic of preeclampsia) has been documented in women with gestational hypertension as well, though milder than in preeclampsia (Stevens et al. 2003). Even AT1-AA levels were intermediate in patients with gestational hypertension between those with preeclampsia (higher) and normotensive pregnancies (low) (Siddiqui et al. 2010). Though not a universal view, these observations speak to diffuse endothelial dysfunction underlying both gestational hypertension and preeclampsia, differing mainly by degree (Noori et al. 2010).

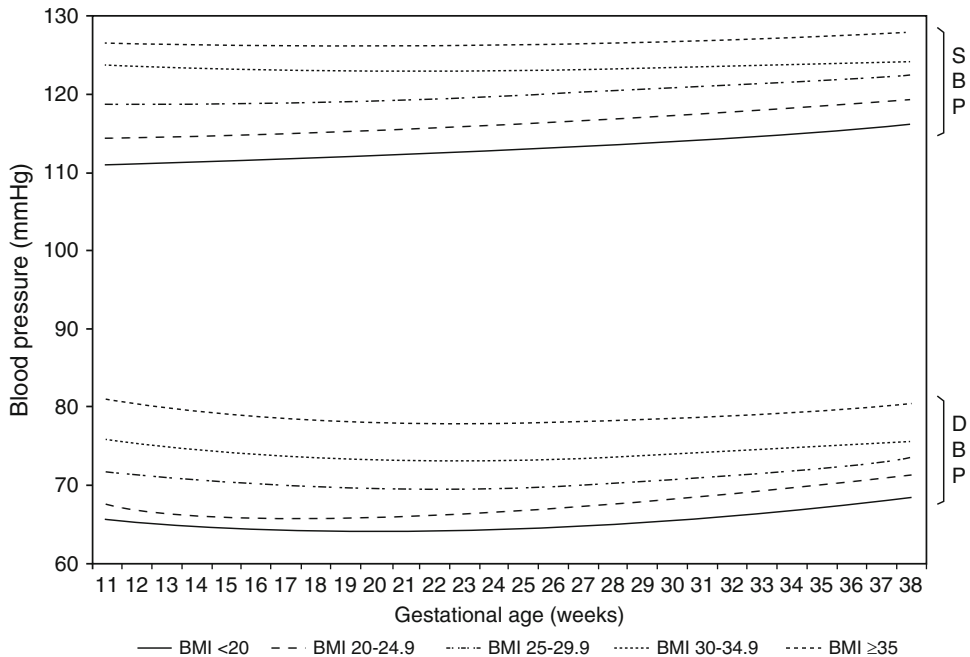
## Risk Factors for Preeclampsia

Risk factors for preeclampsia are listed in Table 2. Although young maternal age was originally thought to increase the risk of gestational hypertension, there is conflicting evidence to support that younger age alone increases the risk of

**Table 2** Risk factors for preeclampsia with relative risk and odds ratio\* (95% confidence intervals)

Nulliparity	2.91 (1.28–6.61)
Previous preeclampsia	7.19 (5.85–8.83)
Previous AKI*	4.70 (2.10–10.10)
Family history of preeclampsia	2.90 (1.70–4.93)
High BMI	
At first evaluation	1.55 (1.28–1.88)
Before pregnancy	2.47 (1.66–3.67)
SBP $\geq$ 130mmHg at first evaluation	2.37 (1.78–3.15)
DBP $\geq$ 80mmHg at first evaluation	1.38 (1.01–1.87)
Preexisting DM	3.56 (2.54–4.99)
Preexisting HTN	Increased risk
Preexisting renal disease	Increased risk

Adapted from Duckitt and Harrington (2005), Steegers et al. (2010), Sibai et al. (1998), Tangren et al. (2016)



**Fig. 4** Blood pressure patterns in different prepregnancy BMI categories (From Gaillard et al. (2011))

gestational hypertension or preeclampsia (some studies did not differentiate between the two outcomes). Younger maternal age was not found to be an independent risk factor in more recent studies (see section on factors unique to the adolescent). The increased risk observed for younger women may be related to several of the known risk factors which are common to the adolescent, including nulliparity, limited sperm exposure, and primipaternity (Duckitt and Harrington 2005). Obesity is a significant risk factor for preexisting hypertension, gestational hypertension, and development of preeclampsia. Results reported from the Generation R Study indicate that higher prepregnancy body mass index (BMI) was associated with greater SBP throughout pregnancy, with the highest levels among the morbidly obese group (Gaillard et al. 2011). There was a pattern of consistently higher SBP and DBP for higher BMI throughout pregnancy (Fig. 4). The odds ratios for gestational hypertension (the term pregnancy-induced hypertension was used) for the overweight/obese/morbidly obese groups as compared to the group with normal BMI were 2.12

(CI 1.54–2.91), 4.67 (3.07–7.09), and 11.34 (6.80–18.86) and for preeclampsia: 1.82 (CI 1.16–2.83), 2.49 (CI 1.29–4.78), and 3.40 (1.39–8.28), respectively (Gaillard et al. 2011). Additionally, greater gestational weight gain was also associated with increased risk of gestational hypertension (<7 g vs. >7 kg) but was not associated with increased risk of preeclampsia. Among the 2637 women participating in the BIRTH study, a dose response effect of BMI on risk of preeclampsia was observed. Indeed, obesity was the most important risk factor for preeclampsia and severe preeclampsia in this cohort, with an attributable risk of 64.9% and 64.4%, respectively (Pare et al. 2014).

Acute kidney injury (AKI) prior to conception significantly increases the risk for preeclampsia. A single center retrospective study over 10 years, including over 25,000 pregnancies, found that the adjusted odds ratio for preeclampsia was 4.7 [2/1–10.1] among women with previous history of AKI and recovery of renal function (no CKD). In addition, risk for adverse fetal outcomes was also significantly increased by prior AKI (OR 2.1, 1.2–3.7] (Tangren et al. 2016).

## Features Unique to the Pregnant Teenager

There are no guidelines as to the definition of gestational hypertension in the adolescent female. The threshold of 140/90 used in adult women is based upon the definition of hypertension for adults in general. It could be argued that this threshold should be decreased for all pregnant women and particularly for adolescent females, because BP levels are lower during the first half of pregnancy (as discussed in previous section). Furthermore, 140/90 is significantly higher than the current definition of stage 1 hypertension among adolescent females (clinic BP at or above the 95th percentile for age and height percentile). A SBP threshold of 140 mmHg is greater than the 99th percentile for females aged 13–17 years of age, whereas the DBP threshold of 90 mmHg approaches the 99th percentile for taller adolescent females. Among a cohort of women with mild gestational HTN, BP levels in teenagers were compared to those of adult women: SBP was  $133.4 \pm 15$  mmHg at the beginning of monitoring for the teenage group and  $139.5 \pm 15$  mmHg for the adult group. Similarly, DBP levels were lower in the teenagers,  $84.1 \pm 13.6$  mmHg versus  $90.1 \pm 11.5$  mmHg in the adults (Barton et al. 1995). A small retrospective study among mothers 15–19 years of age found that a second trimester MAP  $> 80$  mmHg (in contrast to a threshold MAP of 90 mmHg used for adult women) had a sensitivity of 60% and specificity of 93% in predicting gestational hypertension, with a positive predictive value of 76% and negative predictive value of 82% (Gavette and Roberts 1987).

Earlier studies reported a higher incidence of hypertension (preeclampsia/eclampsia) among younger mothers (Treffers et al. 2001; Eure et al. 2002); however, this has been disputed by more recent epidemiologic studies, including a meta-analysis (Sibai et al. 1997; de Vienne et al. 2009; Gupta et al. 2008; Duckitt and Harrington 2005). There was a lower incidence of hypertension in teenage mothers (mean age 18.3, range 13.7–19.9 years) as compared to mothers 20–35 years of age (3.7% vs. 6.6%) (Gupta et al. 2008). The authors did not further classify the underlying hypertension

(i.e., preeclampsia); however, they did subdivide the adolescent group into those aged less than 17 years to investigate whether the very youngest had increased risk and found none. Younger maternal age was associated with a lower risk of preeclampsia in a study of more than 8000 primiparous women at the University Hospital of Caen, France (de Vienne et al. 2009). A systematic review of controlled cohort studies that examined the risk of preeclampsia and age concluded that younger maternal age was not a significant risk factor (Duckitt and Harrington 2005).

A retrospective case-control study using the Finger Lakes Regional Perinatal Data System categorized adolescents (maternal age  $< 19$  years) according to prepregnancy BMI into control (BMI 18.5–24.9  $\text{kg/m}^2$ ), overweight (BMI 25–29.9  $\text{kg/m}^2$ ), obese (BMI 30–34.9  $\text{kg/m}^2$ ), and morbidly obese (BMI  $> 35$   $\text{kg/m}^2$ ). Preexisting chronic hypertension was present in 0.5% of the control group and 1.1% of the combined overweight-obese group. Pregnancy-induced hypertension was present in 4.5% of the control group and 7.8% of the combined overweight and obese group, and preeclampsia in 2.4% of the control versus 4.0% of the overweight and obese group. The odds ratio for gestational hypertension was 1.8 (CI 1.4, 2.3) in women with a BMI  $> 25$   $\text{kg/m}^2$  (Sukalich et al. 2006). This emphasizes the multiple levels of risk associated with the overweight/obese adolescent with respect to pregnancy-associated hypertension: not only are they at increased risk for primary hypertension, they are also at increased risk for pregnancy-related hypertension due to their higher prepregnancy BP levels and BMI.

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## Impact of Chronic Hypertension on Pregnancy Outcome

The prevalence of chronic hypertension among females of child-bearing age appears to be increasing largely due to the increased prevalence of obesity, and this is equally true for the increasing prevalence of hypertension among adolescent females (Wang and Beydoun 2007). Females with chronic hypertension who become pregnant are at

increased risk for developing preeclampsia and of developing preeclampsia relatively earlier in gestation (Seely and Ecker 2011). Preeclampsia occurred in 10–25% of women with mild chronic HTN, with an average prevalence of 20.8% across the four available studies. Chronic hypertension without preeclampsia increases the risk for fetal growth restriction (8–15.5%), preterm birth (12–33.3%), placental abruption (0.7–1.4%), and stillbirth (Seely and Ecker 2011; Sibai et al. 1998). Chronic HTN was associated with a fivefold increase in risk of delivering preterm and 1.5 times increased risk of offspring who are small for gestational age (Seely and Ecker 2011). Although some women with chronic hypertension experience lower BP levels during pregnancy as a result of the typical physiological decrease in BP in the first half of gestation, others develop preeclampsia or worsening hypertension (Sibai et al. 1998). Proteinuria in the setting of chronic hypertension prior to pregnancy is a risk factor for preeclampsia and/or fetal growth restriction (Sibai et al. 1998). It has been recommended that increased risk be assigned to women with chronic hypertension who become pregnant. Women considered to have low risk for developing preeclampsia include those with mild essential hypertension without target organ damage. Among women with chronic hypertension, the higher risk group includes those with secondary hypertension, target organ damage, previous perinatal loss, and SBP > 180 mmHg or DBP > 110 mmHg (Sibai 2002). The case presented at the outset of the chapter illustrates this concept – previous diagnosis of chronic, severe HTN with baseline proteinuria is associated with markedly increased risk for our patient to develop preeclampsia and for her infant to be premature and small for gestational age.

Because of the increased risk of poor outcome in the setting of chronic hypertension, prepregnancy counseling and evaluation is recommended. Prepregnancy counseling is unlikely to be offered in the setting of adolescent pregnancy which is most often unplanned. This raises the question of whether hypertensive adolescents should be counseled regarding the risks that HTN has in the event of pregnancy – this could be added to the warning regarding pregnancy prevention in those taking angiotensin

converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs).

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## Treatment of Hypertension During Pregnancy

The goal for treatment of hypertension during pregnancy is to maintain a healthy BP for the mother while minimizing the risk for the fetus. At the initial visit when pregnancy is diagnosed several important steps should be taken by the provider. The provider should diagnose the duration of pregnancy based on last menstrual period and then stratify the young woman based on other risk factors. A thorough history of chronic disease such as hypertension, diabetes, thyroid disease, or chronic kidney disease should also be elicited. In addition to placing the mother on a prenatal vitamin, the provider should document all medications and herbal supplements being used and then determine if they pose a risk to the mother or fetus. We also assess each patient for certain parameters including nutritional status and food security, risk for domestic violence, substance use, family and social support system, and accessibility to prenatal care. For adolescent women with chronic medical conditions such as hypertension we establish early communication with subspecialist providers to assess any further risks. At the end of the visit we clearly communicate plans for pregnancy options and follow-up care.

Ideally, adolescent females with hypertension should be followed in a clinic where preconception counseling can be offered confidentially and conveniently. Preconception counseling offers the opportunity for both primary care providers and subspecialists to discuss the efficacy and safety of contraceptive methods in conjunction with potential harm from antihypertensive medications (CDC 2012). As a practice, most teens in our clinic that are on potentially teratogenic drugs are placed on some sort of hormonal contraception and are encouraged to use barrier protection as an adjunctive method.

The costs of managing gestational hypertension include the expense of more frequent visits to the obstetrician's office or emergency department,

more frequent laboratory tests and fetal monitoring, as well as hospitalizations, sometimes for prolonged periods (Sibai 2007). In addition, pregnancies complicated by hypertension have higher rates of cesarean delivery and preterm infants who require longer postnatal hospitalization, often in a critical care unit.

Treatment to lower BP during pregnancy is controversial, as guidelines published by different organizations do not agree on the threshold for initiation of treatment or on the goal BP levels after treatment is initiated (Seely and Ecker 2011). The American College of Obstetricians and Gynecologists recommends initiation of antihypertensive therapy if the SBP is  $\geq 180$  mmHg and/or DBP  $\geq 100$  mmHg. The JNC7 Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends initiation of antihypertensive therapy if SBP is  $> 150$ – $160$  mmHg and/or DBP  $> 100$ – $110$  mmHg. Canadian guidelines recommend treatment if the SBP  $> 150$  mmHg and/or DBP  $> 109$  mmHg and the Australasian guidelines for SBP  $> 170$  mmHg and DBP  $110$  mmHg (Seely and Ecker 2011). In contrast, the European Society of Hypertension/European Society of Cardiology guidelines recommend initiation of antihypertensive medication for BP  $\geq 140/90$  (Moser et al. 2012).

In the pregnant female with chronic hypertension, maintenance antihypertensive medications may be continued during pregnancy with the exception of ACEi or ARB, but the recommendations for optimum BP levels are conflicting. The NHBPEP recommendations state that for women with chronic hypertension, antihypertensive medications would not be continued or restarted unless the SBP is  $150$ – $160$  mmHg or DBP is  $100$ – $110$  mmHg. Therefore, according to these guidelines antihypertensive medications might have to be discontinued or modified if BP levels decline. The choice of antihypertensive agent is challenged by paucity of information regarding safety and efficacy of specific agents during pregnancy. The most commonly used antihypertensive drugs during pregnancy include methyl dopa, labetalol, hydralazine, metoprolol, extended-release nifedipine, and hydrochlorothiazide (Seely and Ecker 2011). Methyl dopa is not an agent of choice in adolescents or adult women as

a first or second line agent; however, it is the agent of choice during pregnancy due to its record of safety and proven lack of effect on uterine artery Doppler flow. A Cochrane systematic review of available trials reported a reduction in risk for development of severe hypertension (RR 0.50 (0.41–0.61)) associated with the use of antihypertensive medication to treat mild to moderate gestational hypertension (Abalos et al. 2007). Recent Cochrane analysis now suggests that there is a reduction in the overall risk of proteinuria/preeclampsia when beta-blockers and calcium channel blockers (analyzed together) are compared with methyl dopa (RR 0.73; 95% CI 0.54–0.99) (Abalos et al. 2014). Recommendations from a recent review article include the following two proposals (Moser et al. 2012):

1. For women with chronic hypertension that has been adequately controlled, continue the same medication regimen, with the exception of ACEi and/or ARB
2. For the normotensive female who develops increased BP over  $140/90$  mmHg, initiate treatment with small doses of beta-blockers (labetalol not metoprolol), thiazide diuretic, or calcium channel blocker (in addition to methyl dopa and hydralazine)

Treatment of hypertension reduces maternal morbidity but has no proven effect on fetal outcomes. Treatment to lower maternal BP was not associated with differences between treatment and placebo on fetal outcomes such as preterm birth, intrauterine growth restriction, or fetal death (Abalos et al. 2007). An analysis including 12 trials of the effect of beta blockers (vs. placebo or an agent other than beta blocker) on the incidence of small-for-gestational age infants reported a summary relative risk of 1.36 (1.02–1.82) (Magee and Duley 2003). Beta blockers also increased the risk for neonatal bradycardia (RR 1.93 (1.05–3.53)) and decreased the risk for respiratory distress syndrome (RR 0.29, 0.12–0.67) with no effect on the risk for preterm birth (Magee and Duley 2003). Concerns about overtreatment of hypertension during pregnancy include the potential risk for

reduction of placental blood flow and the exposure of the fetus to potentially teratogenic medications. A meta-analysis of the effect of antihypertensive therapy on fetal outcome reported that every 10 mmHg reduction in MAP resulted in a birth weight reduction of 145 grams (von Dadelszen et al. 2000). This study has been criticized for overestimation of the effect of BP reduction on birth weight (only 16% of variability of birth weight was related to maternal BP) and selection bias, since a trial which indicated an opposite relationship between birth weight and BP reduction was not included (Moser et al. 2012). Since chronic hypertension is associated with significant morbidity for the mother and her baby, one could argue that treatment would be beneficial for both.

The control of hypertension in pregnancy study (CHIPS) trial randomized women with hypertension (defined by DBP) to either tight or less tight BP control to determine whether BP levels were associated with adverse maternal or fetal outcomes. They found comparable primary and secondary outcomes for both groups; however, the incidence of severe hypertension was greater in the less tight control group. There was an association between severe hypertension and serious maternal complications in the less tight control group; this association remained significant after adjusting for presence of preeclampsia. In addition, severe hypertension was associated with low birth weight and preterm delivery among all participants (Magee et al. 2015, 2016). This study raises the question of whether use of ABPM might have characterized BP more completely to avoid misclassification (Bilo and Parati 2016). Editorial comments regarding the CHIPS Trial concluded that tighter BP control does not appear to increase fetal morbidity; in addition thrombocytopenia was more common in the less tight control group (adjusted OR 2.63 [1.1.5–6.05]) as was abnormal elevation of hepatic transaminase levels (adjusted OR 2.33 [1.05–5.16]) (Easterling 2016).

In spite of the CHIPS findings, the ACOG group recommends that the threshold to initiate pharmacologic therapy remain at  $\geq 160/105$ . The agents of choice for oral therapy are labetalol, followed by a calcium channel blocker; the dose

of labetalol should be maximized before adding the second agent. For acute hypertension, they recommend IV labetalol or hydralazine, or oral nifedipine (Amro et al. 2016). The ACOG report recommended labetalol, nifedipine, and methyldopa as first-line agents for treatment of hypertension during pregnancy (2013). The goal for BP for pregnant women with hypertension is 120–160/80–105 mmHg (2013).

As mentioned earlier, ACEi and ARBs should never be used during pregnancy; they increase the risk for fetal developmental abnormalities (Cooper et al. 2006). Fetal renin-angiotensin system blockage syndrome (fetal RAS blockade syndrome) was recognized in the early 1980s as a result of intrauterine exposure to ACEi, originally termed ACE inhibitor fetopathy. Pregnancies in women on ACEi were complicated by oligohydramnios, and infants with the syndrome exhibited intrauterine growth retardation, hypotension, renal failure, and other developmental anomalies. It was initially thought that first trimester exposure was not a risk for the fetus; however, a study which used Medicaid records to link maternal antihypertensive medication use to infant outcomes found increased risk of congenital malformations as compared to exposure to other antihypertensive medication or no antihypertensive medications with a risk ratio of 2.71 (95% CI 1.72–4.27) (Cooper et al. 2006). A systemic review of ACEi and ARB exposure reported the prevalence of fetal RAS blockade syndrome by trimester and duration of exposure (Bullo et al. 2012). Risk for fetal RAS blockade syndrome was lowest for isolated first trimester exposure as compared to exposure during the second and/or third trimesters (Polifka 2012). Based upon the currently available studies first trimester exposure to ACEi or ARB has a similar risk for congenital malformations as exposure to other antihypertensive agents or untreated hypertension during the first trimester (Polifka 2012). Due to concern about fetal risk for congenital malformations due to continued exposure during the second and third trimester, women treated with ACEi or ARB who become pregnant should be treated with alternative anti-hypertensive agents (Polifka 2012).



## Risk of Future Cardiovascular Disease and Renal Disease

The presence of hypertension during pregnancy increases the risk of the woman's and her offspring's future risk of developing cardiovascular disease (CVD). Not only are women with gestational hypertension more likely to develop chronic hypertension, they do so at an earlier age. Women with gestational hypertension also have a greater incidence of coronary heart disease and stroke. Data from women participating in the Family Blood Pressure Program study found that women whose pregnancies were complicated by gestational hypertension demonstrated hazard ratios for stroke of 2.0, for coronary artery disease of 1.5, and for hypertension of 1.5 (Garovic 2012). The adjusted hazard ratio for developing chronic hypertension was 1.88 in a model that controlled for traditional cardiovascular risk factors such as race, family history of CVD, diabetes mellitus, smoking, and dyslipidemia (Garovic et al. 2010). The hazard ratio for stroke after controlling for the aforementioned risk factors as well as hypertension was 2.1. Since the risk factors for developing hypertension during pregnancy may be similar to those risk factors associated with CVD in general, it is unclear whether the association of gestational hypertension and future cardiovascular risk is causal or due to common etiologies.

Recent evidence suggests that preeclampsia may do more than unmask preexisting risk of CVD. A murine preeclampsia model was used in which sFlt was overexpressed in pregnancy leading to hypertension and glomerular disease. Two months postpartum, after normalization of sFlt level, hypertension, and cardiac and renal parameters, the mice were subjected to unilateral carotid artery injury. The injured carotid arteries of animals with prior preeclampsia showed dramatically increased smooth muscle cell proliferation and vascular fibrosis (180% and 216% increase, respectively) compared to those from mice which did not previously have preeclampsia. Notably, no preeclampsia-induced differences were observed in the uninjured carotid arteries. Thus, vessels exposed to preeclampsia had an amplified vascular response to subsequent

injury (Pruthi et al. 2015). These data appear to suggest that after preeclampsia, the vasculature retains a phenotype with the potential for future maladaptive remodeling and increased risk of CVD. Importantly, proteomic analysis of plasma from human mothers with and without preeclampsia showed persistent differences postpartum as well. Thus, 6 months after delivery, the proteome of women with a history of preeclampsia showed altered expression of coagulation cascade factors favoring thrombophilia (increased Factor X and decreased tetranectin) and complement activation, suggesting a potential ongoing link to subsequent cardiovascular risk (Murphy et al. 2015). It is not known whether these or similar alterations in circulating factors may contribute to the observed increased incidence of albuminuria (McDonald et al. 2010) and increased risk of end stage renal disease in mothers with a history of preeclampsia (Vikse et al. 2008; Wang et al. 2013).

Offspring of hypertensive pregnancies are also at risk of developing increased BP. A single center study published in 1979 examined BP of pregnant teenagers during and following pregnancy and BP in their offspring 3–6 years later (Kotchen et al. 1979). Mean BP measured using a mercury sphygmomanometer in the hypertensive group during the mid-third trimester was  $121.4 \pm 1.2/78.8 \pm 0.9$  mmHg compared to  $112 \pm 1.1/69.5 \pm 0.9$  mmHg in the normal group. The postpartum BP levels 3–6 years postpartum remained higher as did maternal weight in the hypertensive group ( $119.4 \pm 2.4/78.3 \pm 1.6$  mmHg) versus the normal group ( $117.1 \pm 1.2/73.4 \pm 1.3$  mmHg). Offspring of the gestational hypertensive mothers had higher mean SBP compared to those with normal maternal BP:  $97.6 \pm 1.3$  versus  $93.1 \pm 1.5$ , at a mean age of 4.5 years.

Gestational hypertension was associated with increased body weight and higher BPs and body weight in the mothers and infants at follow-up. This study is mentioned because it included only pregnant teenagers as part of the Young Mothers' Program at the University of Kentucky and aimed to determine the impact of gestational hypertension on future cardiovascular status (Kotchen et al. 1979). More recently, a meta-analysis which

summarized 18 studies with data from 45,249 individuals reported that in utero exposure to preeclampsia was associated with a 2.39 mmHg increase in SBP and 1.35 mmHg higher DBP during childhood and young adulthood. BMI was increased by 0.62 kg/m<sup>2</sup> after exposure to preeclampsia (Davis et al. 2012). In a study which used data from the Helsinki Birth Cohort Study, adult children born to mothers with preeclampsia and gestational hypertension had a greater risk for stroke with hazard ratio of 1.9 (CI 1.2, 3.0) and 1.4 (CI 1.0, 1.8), respectively. Preeclampsia was also associated with smaller head circumference at birth (Kajantie et al. 2009). In conclusion, females with hypertension during pregnancy – including preeclampsia – appear to have increased risk for significant future cardiovascular morbidity. Furthermore, their offspring have higher BP levels and may also have increased risk for future cardiovascular events as adults.

## Concluding Remarks

Hypertensive disorders of pregnancy represent a major cause of maternal deaths in the USA as well as increased infant mortality and morbidity. Teenagers with chronic hypertension who become pregnant are more likely to be in a higher risk group if they have secondary cause for hypertension such as chronic kidney disease and may also be at greater risk for preeclampsia due to nulliparity and primipaternity. The presence of hypertension during pregnancy increases the future risk for CVD in the mother and her offspring. Exposure to certain antihypertensive medication classes such as ACEi or ARB poses risk for the developing fetus, some of whom have RAS inhibition fetopathy or other congenital malformations. Clinicians caring for the pregnant adolescent with hypertension are challenged by the lack of evidence from which to development guidelines for treatment. Issues which are specific to this unique group include the appropriate threshold for classification as hypertensive (likely to be lower than for adult women during pregnancy), as well as the choice of antihypertensive agents and the goal for BP levels after initiation of therapy.

## Cross-References

- ▶ [Ambulatory Blood Pressure Monitoring Methodology and Norms in Children](#)
- ▶ [Endothelial Dysfunction and Vascular Remodeling in Hypertension](#)
- ▶ [Vasoactive Factors and Blood Pressure in Children](#)

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## Abstract

Young hypertensive adults demonstrate decreased performance on neurocognitive testing compared with that of normotensive controls. There is emerging evidence that children with hypertension also manifest cognitive differences when compared to normotensive controls. Findings from studies of cognition in young adults have important implications for the study of cognition in hypertensive children. Recent studies suggest that both children with primary hypertension and children with hypertension secondary to chronic kidney disease have decreased performance on neurocognitive testing. Furthermore, children with primary hypertension have an increased prevalence of learning disabilities. Potential mechanisms include blunted cerebrovascular

reactivity in hypertensive children. Ongoing studies of cognition in children with primary hypertension will further define the emerging hypertension-cognition link in youth.

## Keywords

Hypertension • Neurocognition • Cerebrovascular reactivity • Brain • Target-organ damage • Chronic kidney disease

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## Introduction

Primary hypertension in childhood is associated with evidence of target-organ damage. Most studies have concentrated on hypertensive cardiovascular effects, showing that children with primary hypertension demonstrate left ventricular hypertrophy (LVH) and increased carotid intima-media thickness (Belsha 1999; Lande et al. 2006). By contrast, there has been a paucity of studies of the effects of hypertension on the brain, with most reports in children being limited to the most obvious neurological manifestations of severe hypertension, such as stroke, seizure, and posterior reversible encephalopathy syndrome (Wong et al. 2011; Sharma et al. 2010). This chapter reviews and updates the emerging evidence that children with hypertension may also manifest subtle abnormalities of cognition.

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## Studies of Cognition in Hypertensive Adults: Implications for Children

Studies in adults show that hypertension is associated with negative effects on cognition, which ranges from mildly decreased performance on neurocognitive testing within the normal range of cognitive functioning to overt dementia (Elias et al. 2012). The finding of decreased performance on neurocognitive testing is most consistently seen in the domains of fluid intelligence, attention, working memory, executive function, and learning and recall of new information (Waldstein et al. 1991, 2001; Waldstein 1995). Furthermore, there is evidence of a genetic predisposition to performance deficits on neurocognitive testing among hypertensive adults with a parental history of hypertension (Pierce and Elias 1993). It is important to note that the lower scores on neurocognitive testing in hypertensive adults represent cognitive deficits only in comparison to those of normotensive controls (Elias et al. 2012). In older adults, cognitive impairment has been associated with changes in diastolic BP (DBP). In a study of 19,836 subjects (mean age, 64.7 years), a higher DBP level was associated with impaired cognition after adjusting

for various demographic characteristics, risk factors, and treatment. A 10 mm increase in DBP was associated with a 7 % higher odds of impairment in cognition (Tsvigoulis et al. 2009).

Review of the literature on adults with hypertension underscores several central observations with particular relevance to studies in children.

- First, reports have shown a more pronounced difference in neurocognitive test performance between hypertensive and normotensive subjects when young adults are studied compared with studies of middle-aged or older hypertensive adults (Waldstein et al. 1996), a finding that lends biological plausibility to the presence of a hypertension-cognition link in children.
- Second, executive function and working memory (a component of executive function) stand out as the most prominent areas where hypertensives demonstrate decreased performance on testing (Waldstein et al. 2001). Executive functions are higher cognitive activities required to organize, implement, and evaluate purposeful, goal-directed behavior. Executive functions are thought to be in maximal use during novel complex tasks where no established routines exist. Components of executive function include organization and planning, problem solving, abstract reasoning, impulse control, and flexible thinking (Pennington and Ozonoff 1996; Straus et al. 2006).
- Third, there are emerging data from several prospective longitudinal cohort studies (Kohler et al. 2014; Yaffe et al. 2014; Yano et al. 2014) and large cross-sectional or retrospective (Gottesman et al. 2014; Li et al. 2014) studies that middle- to late-life cognitive declines associated with hypertension may arise from cardiovascular risk factors, including elevated systolic and diastolic blood pressure, and blood pressure variability that precede cognitive sequelae by decades (and including the young adult years) and involve both the “duration and intensity” of exposure (Yaffe et al. 2014). These data raise concern that with the higher rates of hypertension and elevated blood pressure now being reported among



pediatric populations, the continuum of accruing burden of target end-organ damage to the brain may begin even earlier than previously thought.

## Studies in Children with Primary Hypertension

There is emerging, preliminary evidence that children with primary hypertension manifest neurocognitive differences when compared to normotensive controls (Lande et al. 2012). The relationship between elevated blood pressure (BP) and neurocognitive test performance in children was first investigated in a cross-sectional analysis of 5,077 children 6–16 years old who participated in the National Health and Nutrition Examination Survey III (NHANES III), a nationally representative sample of noninstitutionalized US children and adults (Lande et al. 2003). As part of NHANES III, children were administered a limited battery of four neurocognitive tests: Block Design and Digit Span from the Wechsler Intelligence Scale for Children, Revised (WISC-R), and Reading and Arithmetic from the Wide Range Achievement Test, Revised (WRAT-R). Block Design is a measure of constructional skills, and Digit Span is a measure of auditory attention and working memory (Straus et al. 2006). Children with systolic BP (SBP)  $\geq 90$ th percentile had lower average scores compared with normotensive children for Digital Span, Block Design, and mathematics (Table 1). After adjusting for socioeconomic status, obesity, and other demographic factors, elevated SBP remained

independently associated with lower Digit Span scores ( $p = 0.03$ ). Furthermore, the association between increased SBP and lower Digit Span scores was more pronounced for children with SBP  $\geq 95$ th percentile, suggesting a possible dose effect of BP on cognition.

In a subsequent small, single-center pilot study, 32 children with newly diagnosed, untreated hypertension were compared prospectively to 31 normotensive controls (Lande et al. 2009). Hypertension was confirmed by 24-h ambulatory BP monitoring (ABPM). Hypertensive and control subjects were matched proportionally for factors considered to influence neurocognitive test performance, including socioeconomic status, obesity, and general intelligence (IQ). Parents completed the Behavior Rating Inventory of Executive Function (BRIEF), a rating scale that evaluates executive function skills (e.g., organization, planning) in the context of the child's everyday life (Gioia et al. 2000; Anderson et al. 2002). Specialized questionnaires such as the BRIEF are completed by raters who have observed the child in everyday settings (i.e., parent, teacher). Such rating scales are often used to augment laboratory-based measures of executive function, since mild executive dysfunction may not manifest in the structured, quiet, one-on-one testing environment used for laboratory testing, yet may still impact functioning in real-world settings (Gioia and Isquith 2004). The BRIEF yields two index scores, the Behavior Regulation Index (BRI) and the Metacognition Index (MI), and an overall score that summarizes all item responses, the Global Executive Composite (GEC). The BRI includes items relating to cognitive flexibility, impulse control, and appropriate self-modulation of emotions and behavior. Items in the Metacognition Index relate to skills such as task initiation, organization, planning, maintaining cognitive effort, and self-monitoring one's own cognitive performance. Results are reported as sex- and age-normed T-scores (mean = 50; SD = 10) and higher scores indicate greater degrees of dysfunction.

The study found that BRIEF scores were higher (worse executive function) for hypertensives compared with control subjects. Similar to

**Table 1** Comparison of neurocognitive test scores of participants in NHANES III with SBP  $\geq 90$ th % to those with normal SBP

Cognitive test	SBP <90th %	SBP $\geq 90$ th %	P value
Block design	9.5 $\pm$ 0.10	8.6 $\pm$ 0.35	0.03
Digit span	8.7 $\pm$ 0.08	7.9 $\pm$ 0.24	0.01
Math	93.8 $\pm$ 0.54	89.6 $\pm$ 1.4	0.01
Reading	92.1 $\pm$ 0.53	89.5 $\pm$ 2.3	NS

Mean  $\pm$  SE; NS not significant (Adapted with permission from J Pediatr 2003 Dec;143(6):720–724 (Lande et al. 2003))

**Table 2** Comparison of baseline parent rating scale results of normotensive and hypertensive subjects

Rating scale <sup>a</sup>	Normotensives N = 31	Hypertensives N = 32	P value
<b>BRIEF (T-scores)</b>			
BRI	42.5 (39.5–44.5)	51 (41.5–57.5)	0.014
% in clinical range	3	8	0.43
MI	44 (39–51)	51 (44–56.5)	0.031
% in clinical range	5	6	0.99
GEC	43 (38.5–48)	50 (42.5–57)	0.009
% in clinical range	3	6	0.67
<b>CBCL (T-scores)</b>			
Internalizing	44.5 (36.5–50)	53 (42.5–65.5)	0.022
% in clinical range	6	37	0.005
Externalizing	44 (34–50)	48.5 (41.5–55)	0.087
% in clinical range	6	3	0.99

<sup>a</sup>Median (interquartile range) (Adapted with permission from J Pediatr 2009;154 (2):207–212 (Lande et al. 2009))

observations in adults, both hypertensive and control children obtained scores within the clinically normal range in comparison with same-age peers, and there was no difference in the small proportion of hypertensive and normotensive subjects scoring in the clinically significant range (Table 2).

In the same study (Lande et al. 2009), parents also completed the Achenbach Child Behavior Checklist (CBCL), another parent rating scale that measures a range of childhood emotional and behavioral problems (Achenbach and Rescorla 2001). The CBCL Internalizing Problems scale addresses mood disturbance and social withdrawal, including anxiety and depression. The CBCL externalizing behavior problems scale reflects conflict with others, including aggression, noncompliance, and defiance. Hypertensive children were not different from normotensive controls with regard to externalizing behaviors, but hypertensives had more internalizing behaviors, and more than one-third of hypertensive subjects had internalizing behaviors in the clinically significant range (Table 2). Among hypertensive children, there was also an interaction effect between mood problems and obesity. Internalizing behaviors were highest among hypertensive children who were also obese, suggesting that clinically significant anxiety and depression may be common in children with obesity-associated hypertension.

Another study extended this area of investigation to children with prehypertension

(Ditto et al. 2006). In a post hoc analysis of neurocognitive test performance from a study of the development of aggression in boys, subjects with SBP in the prehypertensive range had significantly lower performance on a spatial learning and memory factor score compared to subjects with lower SBP. In addition, boys with both a parental history of hypertension and SBP in the prehypertensive range had lower performance on a verbal learning factor score. These findings suggest that lower performance on neurocognitive testing may be detectable even in children with prehypertension and that there may be a genetic predisposition to these differences.

The above studies suggest subtle differences in neurocognitive measures between children with elevated and normal BP. The actual clinical significance or functional impact of such mild differences is unclear. However, a recent study showed that children with hypertension do manifest learning and attention problems (Adams et al. 2010). Two hundred and one consecutive children aged 10–18 years referred to a pediatric hypertension clinic for elevated BP were diagnosed with either hypertension ( $n = 100$ ) or prehypertension ( $n = 101$ ). The hypertensive children were more likely than those with prehypertension to be receiving special education services at school for a learning disability (28 vs. 9 %,  $p < 0.001$ ) and were more likely to be receiving medication for attention deficit hyperactivity disorder (ADHD; 20 vs. 7 %,  $p = 0.007$ ). When children with

ADHD were excluded from the analysis, the finding of increased prevalence of learning disability on the hypertension group persisted (20 vs. 7 %,  $p = 0.002$ ). In adjusted analysis, the odds of the diagnosis of learning disability were four times higher in the hypertensive children. The diagnoses of learning disability and ADHD are known to be highly comorbid (Mayes et al. 2000). The authors acknowledged that some of the subjects with ADHD may have had increased BP because they were receiving stimulants for inattention (Samuels et al. 2006), but this relationship between hypertension and learning disability was sustained even after controlling for ADHD and stimulant medication history. As well, the authors postulated that the increased prevalence of ADHD in the hypertensive group may be another indication of neurocognitive difficulties in children with hypertension.

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### Studies in Children with Chronic Kidney Disease

Children with chronic kidney disease (CKD) are at risk for cognitive dysfunction, and over half have hypertension (Flynn et al. 2008). Early studies showed that infants with CKD had high rates of mental retardation, microcephaly, and seizures. With improvement in nutrition and other aspects of medical management, such gross neurodevelopmental problems are now uncommon (Gerson et al. 2006). However, some children with CKD are still found to show lower intellectual abilities compared to children without renal disease, particularly with regard to intelligence quotient, academic achievement, attention regulation, or executive functioning (Hooper et al. 2011).

Relationships between cognition and hypertension were recently evaluated in the Chronic Kidney Disease in Children (CKiD) study population, a cohort of children with mild-to-moderate CKD (Lande et al. 2011). CKiD subjects underwent both auscultatory BP determination and an extensive neurocognitive test battery. Elevated BP was defined as SBP and/or diastolic BP (DBP) >90th percentile, regardless of whether the subject was on antihypertensive medication. Subjects with

elevated BP had worse performance IQ (PIQ) scores on the Wechsler Abbreviated Scales of Intelligence compared with subjects with normal BP (92.4 vs. 96.1,  $p = 0.03$ ). Furthermore, elevated BP remained independently associated with lower PIQ score, after adjusting for severity of CKD and other potential confounders. There was no difference between groups on measures of attention, verbal IQ, academic achievement, or parental ratings of executive function. The authors concluded that children with CKD may have difficulties with visual-spatial organization and visuoconstructive abilities that are related, in part, to elevated BP.

A more recent single-center study of cognition in children and young adults with CKD extended the evaluation of the role of hypertension by including 24 h ambulatory BP monitoring. Neurocognitive test performance of 90 subjects with CKD aged 8–25 years was compared to that of 70 control subjects. After adjusting for sociodemographic characteristics and estimated GFR, increased diastolic BP load was associated with worse performance on tests of language ( $z$  score  $\beta = -0.076$ ,  $p = 0.05$ ) and verbal memory ( $\beta = -0.166$ ,  $p = 0.02$ ). Furthermore, blunted diastolic nocturnal dipping was associated with lower scores on measures of attention ( $\beta = 0.017$ ,  $p = 0.04$ ). The authors concluded that hypertension may be an important and potentially modifiable risk factor in decreased neurocognitive function in youth with CKD (Ruebner et al. 2016). While the mechanism of hypertension leading to neurocognitive deficits was unclear, the same subjects also underwent multimodal magnetic resonance imaging (MRI) to assess brain structure, function, and blood flow to explore the neurologic impact of hypertension in children with kidney disease (Hartung et al. 2015). However, these highly anticipated results are as yet unpublished at the time of this chapter.

Studies in adults show that alterations in BP have negative impact on health not only through elevations in mean BP but also through increases in BP variability (Parati et al. 2012). Increased BP variability in adults is associated with decreased performance on neurocognitive testing (Havlik

et al. 2002; Yano et al. 2014). A recent study of CKiD subjects  $\geq 6$  years old evaluated the association between increased BP variability and neurocognitive test performance (Lande et al. 2016). Blood pressure variability was assessed using the standard deviation of visit BPs (BPV-SD) and average real variability (ARV). Subjects with systolic visit-to-visit BP variability in the upper tertile scored lower on the Delis-Kaplan Executive Function System (D-KEFS) verbal category switching test compared with subjects with BP variability in the lower tertile (BPV-SD, 8.3 vs. 9.5,  $p = 0.006$ ; ARV, 8.5 vs. 9.6,  $p = 0.02$ ). The association between lower category switching score and increased BPV remained significant after controlling for mean BP, demographic characteristics, and disease-related variables. Category switching falls within a group of executive function tasks called set shifting – the mental ability to adjust thinking or attention in response to changing expectations, goals, or environmental stimuli (Lande et al. 2003). The investigators concluded that children with CKD may have difficulties with this component of executive functioning that are related, in part, to increased BP variability.

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## Studies of Antihypertensive Therapy

If the lower performance on neurocognitive measures seen in adults with hypertension represents an early manifestation of target-organ damage to the brain, then one might expect that such deficits would improve after treatment with antihypertensive medication. However, results of adult studies on the effect of antihypertensive medication on cognition have been inconsistent in the existence and direction of drug effects (Muldoon et al. 1991, 1995). Studies have had significant methodological weaknesses, and most have focused on older adults, a group more subject to the potential confounding effects of aging. Most studies have been small, have used limited neurocognitive measures, or have not controlled for practice effects (the propensity of scores to improve due to repeat test administration). In a recent study designed to address previous methodological

flaws in this area, adults aged 25–55 years with primary hypertension were randomized to receive a 6-week course of a single antihypertensive medication followed by another 6-week course of a different antihypertensive medication after a 2-week washout period (atenolol followed by metoprolol, methyldopa followed by thiazide, enalapril followed by verapamil). Comprehensive neurocognitive assessment occurred at baseline and again after completing the 6-week course of each antihypertensive medication. A normotensive control group received the same neurocognitive assessments over the same time period in order to estimate practice effects. The results showed that the antihypertensive medications slightly improved performance on tests of memory but also resulted in small decrements in psychomotor speed, without drug-class differences (Muldoon et al. 2002).

Data on the effects of antihypertensive therapy on neurocognitive measures in children are limited. One single-center study reported on the change in parent ratings of executive function in hypertensive children after 12 months of antihypertensive therapy (therapeutic lifestyle modification, ACE inhibition) (Lande et al. 2010). The subjects in this report were the participants from the prior study of baseline parental assessments described above (Lande et al. 2009), who subsequently returned for reassessment after 12 months. The sample size was small (hypertensives,  $n = 22$ ; controls,  $n = 25$ ) due to a relatively high dropout rate. Scores on the parent BRIEF improved in hypertensive subjects but not controls, with scores being statistically indistinguishable between groups at 12 months (Table 3). Furthermore, subjects felt to be most at risk for target-organ damage (baseline left ventricular hypertrophy and/or systolic BP load  $\geq 50\%$  on ABPM) were more likely to show improvement in BRIEF scores (executive function) after antihypertensive therapy. Neither hypertensive nor control subjects had significant change in CBCL scores from baseline to 12 months, suggesting that the improvement in parent ratings of executive function on the BRIEF in the subjects with hypertension was not simply a false-positive finding caused by parents' nonspecific expectation

**Table 3** Comparisons of parent rating scale T-scores, adjusted for age and socioeconomic status, from baseline to the 12-month assessment

Parental assessment	Control <i>N</i> = 25			Hypertensive <i>N</i> = 22		
	Baseline	Follow-up	P value	Baseline	Follow-up	P value
<b>BRIEF</b>						
BRI	42.1 ± 3.3	42.2 ± 3.4	0.55	50.3 ± 9.4	46.2 ± 8.5	0.01
MI	44.2 ± 7.7	45.0 ± 8.6	0.86	52.4 ± 11.8	46.3 ± 7.7	<0.01
GEC	42.8 ± 6.0	43.4 ± 7.1	0.84	52.1 ± 12.1	46.1 ± 8.3	<0.01
<b>CBCL</b>						
Internalizing	45.2 ± 9.5	43.4 ± 10.5	0.24	54.9 ± 12.7	52.2 ± 11.9	0.12
Externalizing	42.2 ± 8.2	41.8 ± 8.5	0.50	48.1 ± 7.8	45.5 ± 9.4	0.08

Adapted with permission from *J Pediatr* 2010 Jul;157(1):114–119 (Lande et al. 2010)

that their children improved with antihypertensive therapy.

### Potential Mechanisms: Studies of Cerebrovascular Reactivity

Potential mechanisms of how high BP can alter behavior and cognition are beginning to receive attention. Cognitive processing elicits a regional distribution of blood flow, providing metabolic support to active neural areas. Hypertension can affect small vessels that result in vascular remodeling and impairment of cerebral blood flow regulation. The so-called vascular hypothesis of cognitive dysfunction suggests that hypertension may interfere with this redistribution of blood flow or decrease the ability to enhance cerebral blood flow in response to increased neuronal activity. This altered process might underlie the cognitive deficits of hypertensive individuals (Jennings 2003).

The capacity of cerebral blood vessels to dilate in response to different factors has been defined as cerebrovascular reactivity and may be an important marker for brain vascular reserve. Different methods to assess cerebral hemodynamics (e.g., transcranial Doppler [TCD], magnetic resonance imaging) using different reactivity stimuli (e.g., carbon dioxide, hyperventilation) have been utilized to characterize the physiological association between hypertension and cerebrovascular reactivity (Maeda et al. 1994; Leoni et al. 2011). These methods have shown impairment in the carbon dioxide reactivity (the cerebrovascular response

to changes in the arterial pressure of carbon dioxide) in both hypertensive animals and hypertensive human subjects compared to normotensive controls.

In children, there are few studies that have studied the effects of hypertension on cerebrovascular reactivity to assess changes in cerebral blood flow in response to different stimuli (Table 4). One hundred and thirteen hypertensive (mean age 16.4 years) and 58 normotensive (mean age 15.8 year) adolescents were studied at rest and after 30 s of breath-holding (breath-holding test), as a vasodilatory stimulus (Settakias et al. 2003), and at rest and after 60 s of voluntary hyperventilation, as a vasoconstrictor stimulus (Settakias et al. 2006). Hypertension was defined by the average of nine casual BP measurements on three different occasions. The middle cerebral artery (MCA) was insonated through the temporal window on both sides. Hypertensive subjects showed decreased of both vasodilatory and vasoconstrictor ability of the cerebral arterioles, consistent with decreased cerebrovascular reactivity among hypertensives compared to healthy controls.

In a subsequent study, young participants were divided according to findings on 24 h ABPM. Seventy-three subjects with ambulatory hypertension (mean age 16.5 years) and 47 with white coat hypertension (mean age 16.3 years) were compared to 59 normotensive controls (mean age 15.8 years). Cerebrovascular reactivity was assessed by TCD breath-holding test and expressed in percent change to the resting cerebral blood flow velocity value (Pall et al. 2011). Reactivity to carbon dioxide (CO<sub>2</sub>) was diminished in

**Table 4** Cerebrovascular reactivity prospective studies in young hypertensive subjects

Publication	Population	Main results
Settakis et al. (2003)	58 normotensive and 113 HT adolescents	HT had higher resting blood flow velocity parameters and these differences disappeared after breath-holding test SBP $122.2 \pm 23.7$ vs. $114.8 \pm 27.6$ , $p = 0.07$ (HT vs. control) DBP $52.0 \pm 16.4$ vs. $53.1 \pm 16$ , $p = 0.67$ (HT vs. control)
Settakis et al. (2006)	58 normotensive and 113 HT adolescents	Change in flow velocities was decreased in HT vs. controls Systolic blood flow $21.0 \pm 19.0$ vs. $25.9 \pm 12.5$ , $p < 0.05$ Diastolic blood flow $40.4 \pm 18.1$ vs. $45.5 \pm 15.2$ , $p < 0.05$
Pall et al. (2011)	59 normotensive, 47 WCH, and 73 HT adolescents	Mean blood flow velocity change was lower in WCH = $5.3 \pm 3.1$ % and HT = $9.5 \pm 2.6$ % compared to normotensive controls = $12.1 \pm 2.2$ %
Wong et al. (2011)	9 normotensives, 9 preHT, 18 WCH, and 13 untreated HT and 7 treated HT children and adolescents	TCD reactivity was lower in untreated HT = $2.556 \pm 1.832$ cm/s/mmHg compared to normotensive controls = $4.256 \pm 1.334$ cm/s/mmHg ( $p < 0.05$ )
Ostrovskaya et al. (2015)	4 prehypertensives 10 hypertensives	Blunted cerebrovascular reactivity was associated with worse parental ratings of executive function

Adapted with permission from *Pediatr Nephrol* 2012 Jun  
HT hypertensive, WCH white coat hypertension

both white coat and hypertensive subjects, compared to controls, also suggesting abnormal cerebrovascular reactivity.

In another study, 56 children and adolescents, from 7 to 20 years of age (mean age 15.3 years), were classified according to 24 h ABPM as hypertensive, prehypertensive, or white coat hypertensive and compared to normotensive controls. They were evaluated by TCD examination of the MCA while rebreathing CO<sub>2</sub>. Cerebrovascular reactivity during hypercapnia was quantified by time-averaged maximum mean cerebral blood flow velocity and end-tidal CO<sub>2</sub>. This study also found that children and adolescents with untreated hypertension had significantly lower hypercapnic reactivity compared to normotensive controls (Wong et al. 2011).

In adults, as hypertension is associated with both a decline in cognitive function and decreased responsiveness to carbon dioxide, it has been hypothesized that altered vasoreactivity is associated with lower executive function (Hajjar et al. 2014). In children, given that alterations in

cerebral blood flow and possible neurocognitive deficits have been described in other diseases (e.g., sickle cell disease (Kral et al. 2003), mild-disordered breathing (Hill et al. 2006)), it has been suggested that the neurocognitive deficits described in hypertension may be secondary to abnormal cerebrovascular reactivity as well (Wong et al. 2011). Recently, pediatric researchers correlated the results of TCD reactivity slopes with executive function as measured by the parent Behavior Rating Inventory of Executive Function (BRIEF) in a small subset of children ( $n = 14$ ) (Ostrovskaya et al. 2015). The TCD reactivity slopes had a significant inverse relationship with BRIEF scores [Behavioral Regulation Index ( $r = -0.60$ ,  $P = 0.02$ ), Metacognition Index ( $r = -0.40$ ,  $P = 0.05$ ), and the Global Executive Composite ( $r = -0.53$ ,  $P = 0.05$ )]. While the sample size was small, these preliminary results suggest that children with elevated blood pressure may have decreased executive function that is associated with blunted cerebrovascular reactivity, same as in adults.

In summary, preliminary studies have demonstrated that children and adolescents with hypertension have abnormal response to various reactivity stimuli, suggesting abnormal cerebrovascular reactivity as a result of elevated BP. All of these studies have limitations, especially the low numbers of subjects. It is not known whether these effects of hypertension on the cerebral vessels have a cause-and-effect relationship or whether it is an epiphenomenon. Ongoing research will help clarify the relationship among elevated BP, abnormal cerebrovascular reactivity, and neurocognitive deficits in children and adolescents.

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## Challenges

There are several unique challenges in the area of BP, behavior, and cognition that should be acknowledged. Hypertension is commonly associated with obesity in children, an entity that is also associated with disordered sleep, which in turn is itself associated with decreased performance on neurocognitive testing and academic difficulties (Beebe et al. 2010). Recently, disordered sleep was associated with worse scores on rating scales of executive function in a study of children with primary hypertension (Lande et al. 2015). Therefore, studies of cognition in hypertension need to carefully control for obesity. In addition, since the difference in performance on neurocognitive testing between hypertensives and controls tends to be relatively small in magnitude and often occurs within the normal range of the neurocognitive tests, such findings may be overshadowed by subject characteristics that more strongly influence performance on tests of cognition, such as parental education, socioeconomic status (Straus et al. 2006), depression (Jonas and Lando 2000), and anxiety (Straus et al. 2006). Therefore, studies of cognition in childhood hypertension need to also control carefully for these confounding variables.

Furthermore, results of studies comparing neurocognitive test scores before and after antihypertensive therapy may be influenced by practice effects, the propensity for scores to improve due to

repeated test administration (Straus et al. 2006). In addition, investigators need to consider that there may be direct central effects of antihypertensive medications on the brain. As an example, the brain has its own renin-angiotensin system, suggesting potential direct central nervous system effects on cognition by angiotensin-converting enzyme inhibitors (von Bohlen und Halbach and Albrecht 2006). Finally, subject motivation and effort during neurocognitive testing can vary from assessment to assessment, even within the same subject. Neurocognitive test data can be invalidated when subjects are disinterested in the testing or not well rested on the day of the assessment, a particular challenge in studies involving adolescent subjects. An ongoing multicenter study of cognition in children with primary hypertension was designed to specifically address many of these challenges (Lande et al. 2013).

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## Implications and Conclusions

The practical implications of the subtle differences in neurocognitive measures between hypertensive and normotensive children detailed above are not known. Reports to date are limited to database studies, small single-center studies, and post hoc analyses. In addition, the reported cross-sectional analyses do not allow inference about causality. Hypertension could be leading to neurocognitive deficits, as an early manifestation of hypertensive target-organ damage to the brain. Alternatively, children with neurocognitive abnormalities could be more prone to develop hypertension, a disease which is known to be, in part, centrally mediated (Sorof et al. 2002).

The preliminary findings detailed in this chapter provide evidence that children with hypertension may (1) manifest decreased scores on measures of neurocognition, (2) have an increased prevalence of learning difficulties, (3) have an increased prevalence of depression and anxiety, and (4) have altered cerebrovascular reactivity. Larger studies using more extensive neurocognitive measures and broader neuroimaging techniques are needed to confirm the presence of a hypertension-cognitive link in children, to

better delineate the long-term behavioral and cognitive impacts of childhood-onset hypertension, and to potentially guide antihypertensive therapy decisions.

## Cross-References

- ▶ [Hypertension in Older Adolescents and Young Adults](#)
- ▶ [Obstructive Sleep Apnea and Hypertension](#)
- ▶ [Sequelae of Hypertension in Children and Adolescents](#)

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## Abstract

In most children elevated blood pressure measurements are transient and due to situational anxiety. When the blood pressure elevations persist, most children are found not to have an identifiable cause for the hypertension. In the minority of children, hypertension is due to an identifiable cause which may include a variety of medications and illicit substances. Substance-induced hypertension can be associated with unexpected and severe blood pressure elevations and should be considered in such circumstances. Fortunately, the blood pressure typically returns to normal values soon after stopping the offending agent, and usually pharmacologic intervention is not required.

## Keywords

Hypertension • Children • Substance-induced • Stimulants • Illicit drugs • Club drugs • NSAIDs • Phenylephrine • Pseudoephedrine • Anti-VEGF

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## Introduction

High blood pressure in children and adolescents is usually attributable to essential hypertension, obesity-related hypertension, and, less commonly, secondary forms of hypertension such as renal or renovascular disease (Welch et al. 2012; Gupta-Malhotra et al. 2015). Infrequently, children may present with acute and potentially life-threatening increases in blood pressure (BP) following exposure to a diverse group of legal and illicit pharmacologic agents. While hypertension can result from a standard dose of an appropriately prescribed medication, a sudden, unexpected, and marked increase in BP should cause the clinician

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to consider the possibility of an exposure to an illicit substance, herbal compound, or the misuse of a legally prescribed medication. Substance-induced hypertension generally refers to hypertension caused by intoxicating, stimulating, or narcotic chemicals or drugs. A broader definition embraces other nonprescription compounds known to increase BP such as tobacco, caffeine, alcohol, herbal products, and anabolic steroids.

## Medication-Induced Hypertension

In both the ambulatory and inpatient setting, children are routinely exposed to a multiplicity of prescription medications and therapeutic agents. With any pharmaceutical product, there may be undesired effects, such as hypertension, observed with the use of these products in the clinical setting. Drug-induced hypertension may materialize through a variety of mechanisms (Table 1) by means of a direct effect of the drug, a drug-food interaction (e.g., MAOIs), or a drug-drug interaction. It is estimated that during any month, one out of every four children receives at least one prescription medication and 3.5% receive three or more (Health, United States 2015: With Special Feature on Racial and Ethnic Health Disparities). Unlike prescription drugs, readily available over the counter (OTC) medications are not captured in insurance or pharmacy claims, and accurate estimates of exposure are limited. One phone survey of US homes indicated that children are routinely given OTC medication products. In any given week, 56% of children receive at least one medicine product (OTC, prescription, herbal), 10% a cough or cold product, and <1% an herbal product (Vernacchio et al. 2008, 2009). Compared to children receiving care in the ambulatory setting or at home, hospitalized children are exposed to a

far greater number of medications, and those medications are more likely to include hypertension as an adverse effect (Feudtner and Dai 2012). Medication products frequently associated with hypertension are listed in Table 2, and a selected few are discussed in further detail below. Each day, a hospitalized child receives, on average, five different therapeutic agents and during a 7-day hospitalization may have a cumulative exposure of up to 20 different compounds. The number of medications received by children with more complex or unique diagnoses (e.g., cancer) can be even higher (Feinstein et al. 2014).

Fortunately, medication-induced hypertension generally improves or resolves when the offending medication is stopped or when there is a reduction in the dosage. In severe cases (e.g., serotonin syndrome) the BP response to medication withdrawal may be delayed. In those cases, the hypertension should be managed with short-acting drugs to avoid excessive BP lowering once the crises has stabilized. At times, the medicine contributing to the hypertension is vital to the treatment and cannot be stopped, such as the use of the immunosuppressant calcineurin inhibitors in transplant patients. In those circumstances, an antihypertensive medication can be added in order to lower the BP to the normal range while continuing the causative agent. As there are no studies evaluating the relative effectiveness of specific antihypertensive agents in medication-induced hypertension, when needed, it seems reasonable to initiate treatment with an antihypertensive agent that targets the presumed mechanism of action (Table 2).

## OTC Sympathomimetic Medications

OTC sympathomimetic agents (e.g., phenylpropanolamine, pseudoephedrine, and phenylephrine) have been used for years to treat the nasal congestion associated with upper respiratory tract infections and allergic rhinitis. In the past decade, phenylephrine has largely replaced phenylpropanolamine and pseudoephedrine as the sympathomimetic compound of choice in cough and cold products. Phenylpropanolamine was voluntarily

**Table 1** Mechanisms of drug-induced hypertension

- |   |
|---|
| 1. Volume retention                             |
| 2. Activation of the sympathetic nervous system |
| 3. Activation of the renin-angiotensin system   |
| 4. Direct vasoconstriction                      |
| 5. Unknown                                      |

**Table 2** Medication products commonly associated with hypertension

Category	Examples	MOA
<b>Adrenal steroids</b>		
Androgens	Testosterone	Unknown (? renal vasoconstriction)
Glucocorticoids	Methylprednisolone, prednisolone, dexamethasone	Multifactorial
Mineralocorticoids	Fludrocortisone	↑ Salt and H <sub>2</sub> O absorption
Sex hormones	OCP, estrogens	Multifactorial
<b>Adrenergic agents</b>		
Alpha-agonist	Phenylephrine, dobutamine, ephedrine, norepinephrine	↑SNS activity
<b>Anesthetics</b>		
Dissociative	Ketamine	↑SNS activity
Adrenergic agonist	Dexmedetomidine	↑SNS activity
<b>Antidepressants</b>		
SSRI	Venlafaxine	↑SNS activity
Tricyclic	Amitriptyline, imipramine	↑SNS activity
MOA inhibitors	Selegiline	↑SNS activity
<b>Anti-infective</b>		
Antimycotic	Ketoconazole	↑ Salt and H <sub>2</sub> O absorption
HAART	Antiretrovirals	Unknown
<b>Antineoplastic</b>		
Aromatase inhibitors	Anastrozole, exemestane	Unknown (? renal vasoconstriction)
Tyrosine kinase inhibitors	Sorafenib, lenvatinib	↓Nitric oxide production ↓Microvessel density (↑PVR) Activation endothelin-1
<b>Blood modifiers</b>		
Erythropoietic	Epoetin alfa, darbepoetin alfa	Multifactorial
<b>CNS stimulants</b>		
Amphetamine	Amphetamine, dexamethylphenidate, lisdexamfetamine, dextroamphetamine, methylphenidate	↑SNS activity
<b>Immunosuppressants</b>		
Calcineurin inhibitors	Cyclosporine, tacrolimus	Direct vasoconstriction

SSRI selective serotonin reuptake inhibitor, MAOI monoamine oxidase inhibitor, HAART highly active antiretroviral therapy, SNS sympathetic nervous system

removed from the market in 2000 after it was associated with hemorrhagic strokes (Kernan et al. 2000), and access to pseudoephedrine was greatly restricted with the Combat Methamphetamine Epidemic Act of 2005.

While hypertension is listed as a potential adverse effect of nonprescription phenylephrine and pseudoephedrine, when used by adults within the recommended dosing parameters for cold symptoms, there does not appear to be a clinically meaningful increase in blood pressure. Meta-

analyses of oral phenylephrine (Hatton et al. 2007) and pseudoephedrine (Salerno et al. 2005) found that while there is a statistically significant increase in systolic BP, the typical rise in BP is only around 1 mmHg, and there is no change in diastolic BP. A similar blood pressure response, that is, a minimal rise in SBP (+1 mmHg) and no change in DBP, was observed in patients with stable, treated hypertension who received pseudoephedrine (Salerno et al. 2005). Although the studies to date have not shown an appreciable

cardiovascular effect of OTC oral sympathomimetic agents, the studies have mainly been conducted on healthy adults, and the potential for clinically significant changes in blood pressure in children remains possible.

### **Nonsteroidal Anti-inflammatory Drugs (NSAIDs)**

NSAIDs are a group of drugs that are commonly used for their analgesic and antipyretic effect. NSAIDs inhibit the activity of cyclooxygenase (COX-1 and COX-2) blocking the conversion of arachidonic acid to prostaglandins and thromboxane. The isoenzyme COX-2 plays the predominant role in inflammation, and its inhibition is key to the therapeutic effect of NSAIDs.

Adult trials have found an association between the chronic consumption of NSAIDs and increases in blood pressure (Aw et al. 2005; Johnson et al. 1994, 2003; Aljadhey et al. 2012). While the increase in blood pressure in those without preexisting hypertension appears to be minimal (around 1 mmHg), the BP rise in hypertensive patients taking antihypertensive medications is clinically significant with a typical blood pressure increase of 5 mmHg. The selective COX-2 inhibitors may be more likely to cause a rise in BP than the nonselective agents (Aw et al. 2005). Further analyses have also suggested that NSAIDs may have a differential effect on blood pressure based on the type of antihypertensive medication that is prescribed to control blood pressure (Aljadhey et al. 2012). The greatest magnitude of BP rise with NSAIDs occurs with beta-blockers with lesser effect in those taking angiotensin-converting enzyme inhibitors, calcium channel blockers, and diuretics. The varied degree to which prostaglandins mediate the antihypertensive effects of different classes of agents is a proposed mechanism for the differential effects observed with NSAIDs. The impact of NSAIDs on blood pressure in children with and without hypertension is not available, but in view of the adult data the chronic use of NSAIDs in children with hypertension should be used with caution.

### **Anti-vascular Endothelial Growth Factor (VEGF) Medications**

Drugs that target the vascular endothelial growth factor (VEGF) are increasingly being explored for the treatment of various malignancies. Currently the group of drugs includes humanized monoclonal antibodies directed against VEGF-A (bevacizumab) and small molecule tyrosine kinase inhibitors which target VEGF receptors (e.g., sunitinib, sorafenib, pazopanib). VEGF is an important compound that helps maintain homeostasis of the vascular endothelium. Anti-VEGF therapy causes endothelial dysfunction and is commonly associated with hypertension. In adults, hypertension has been noted in 11–43% of patients, but in some settings the incidence of hypertension may be as high as 90% (Hayman et al. 2012). In fact, the development of hypertension may be an independent predictor for survival and is considered by some to be a surrogate marker of the effectiveness of VEGF blockade (Mir et al. 2009). In children, anti-VEGF therapy has been explored in some phase 1 and 2 studies with a reported 11–69% incidence of hypertension (Reismuller et al. 2010; Benesch et al. 2007; Gururangan et al. 2012; Bender et al. 2008; Hwang et al. 2013; Widemann et al. 2012; Kim et al. 2012). The risk of developing hypertension with therapy appears to be dose related and associated with drug potency and drug specificity for the tyrosine kinase receptor. Although the hypertension usually improves upon stopping the drug, there are reports of the hypertension persisting after drug removal.

The hypertension associated with anti-VEGF therapy is proposed to result from the inhibition of nitric oxide and prostacyclin release resulting in vasoconstriction. Anti-VEGF therapy also reduces the density of microvascular networks (e.g., rarefaction) leading to an increase in systemic vascular resistance (Hayman et al. 2012).

There are no established guidelines on the treatment of hypertension that originates for anti-VEGF drugs. Calcium channel blockers are preferred with the exception of nifedipine which may induce VEGF secretion and verapamil and diltiazem which may inhibit the CYP3A4 metabolism

of the tyrosine kinase inhibitors leading to increased drug exposure. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have also been advocated, in part due to the potential proteinuria effect of anti-VEGF drugs (Hayman et al. 2012).

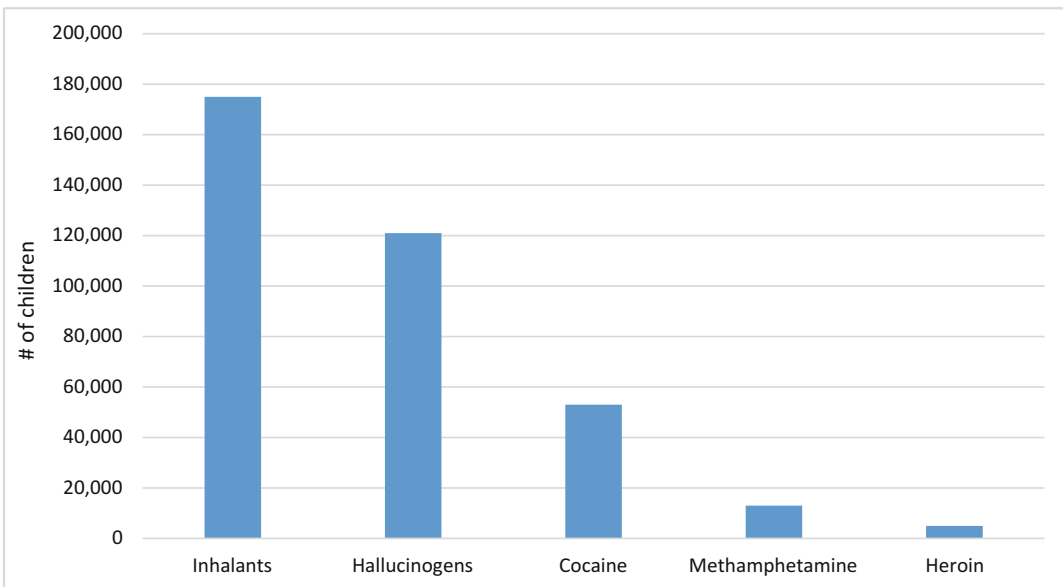
## Substance-Induced Hypertension

Pediatric exposure to illicit drugs is not trivial, especially for those in the adolescent age group (12–17 years). In 2015 it is estimated that there were 2.2 million teens who were current users of illicit drugs (Fig. 1) (2016 HHS Publication No. SMA16-4984 2016). Many children, especially young children where exposure to an illicit drug is often accidental, present to the emergency department (ED) with signs and symptoms of a toxidrome that may include hypertension. Of the illicit drug-related ED visits for children, cocaine and other stimulants accounted for approximately three-fourths ( $n \sim 12,000$ ) of all illicit drug-related ED visits in 2011. MDMA (ecstasy) accounted for 3184 ED visits, and 1722 ED visits were associated with exposure to a hallucinogen (Emergency Department Data 2011).

Illicit drugs commonly associated with hypertension are listed in Table 3 and include stimulants, club drugs, hallucinogens, and dissociatives. The true incidence of hypertension associated with illicit drug use is largely unknown, and the association linking drug exposure to hypertension is usually based on anecdotal evidence made available through case reports and case series. Identifying those exposed to an illicit drug is hampered by a reluctance of those seeking care for themselves or their children to disclose illicit drug use or the presence of illicit drugs in the home due to legal ramifications. Variations in drug purity and composition pose an additional challenge in assigning a cause and effect relationship between a specific illicit drug and hypertension. By nature of the illegal manufacturing enterprise, the chemical composition of the proposed drug may range in purity from one source to another, may be contaminated by adulterants that may themselves cause hypertension, or may be a completely different drug compound than assumed by the user.

## Stimulants

Stimulants are psychoactive drugs that induce transient increases in alertness, attention, and



**Fig. 1** 2015 estimated current use of illicit drugs in US Teens

**Table 3** Commonly abused drugs associated with hypertension

Substance	Example
Club drugs	MDMA (ecstasy), GHB
Dissociatives	PCP, ketamine
Hallucinogens	LSD, mescaline
Stimulants	Cocaine, amphetamine, methamphetamine, caffeine, Ma Huang ( <i>Ephedra sinica</i> )
Other	Alcohol, nicotine, anabolic steroids

energy, as well as elevate BP, heart rate, and respiration. Common stimulants associated with hypertension include cocaine, amphetamine and amphetamine derivatives, caffeine, and the herbal product Ma Huang (*Ephedra*).

Stimulants are the most common group of illicit drugs linked to hypertension although the exact incidence of stimulant induced hypertension is difficult to establish due to the difficulties presented earlier. BP is not mentioned in most of the pediatric case reports, but in one series of children exposed to cocaine, the majority of symptomatic children displayed hypertension (Shannon et al. 1989). In a prospective observational study of adults presenting to an urban ED with a diastolic BP greater than 120 mmHg and no clear pre-existing cause, 13.1% tested positive for cocaine (Givens et al. 2007). In otherwise healthy individuals, the net increase in BP that is described with cocaine exposure is an increase in the systolic BP and diastolic BP of around 20 and 10 mmHg, respectively (Menon et al. 2007; Eisenbert et al. 1993). Despite the relatively moderate increase in BP seen in most adults exposed to cocaine, some individuals can have extreme increases in blood pressure (Secemsky et al. 2011). Some of the variation observed in the magnitude of BP response may be related to the dose and formulation of cocaine (e.g., IV, nasal, smoked) as well as patient characteristics. For example, in a group of adult patients with preexisting, well-controlled hypertension, smoking cocaine had a more pronounced effect on BP than reported in generally healthy individuals (Secemsky et al. 2011). In this group of hypertensive patients, cocaine resulted in an average increase in systolic BP of 74 mmHg and diastolic BP of 30 mmHg. Eight out of the ten

patients studied developed a diastolic BP that exceeded 110 mmHg. One hypothesis forwarded to explain this exaggerated response is that certain groups of patients, possibly those with underlying chronic conditions (e.g., hypertension, heart failure, and chronic kidney disease), may have a disease-associated decrease in the usual baroreceptor reflex response that would normally serve to lower the BP increase that was induced by cocaine. The decreased effectiveness of the BP lowering reflex leads to an exaggerated increase in blood pressure. In addition to hypertension, cocaine is associated with other forms of cardiovascular toxicity such as myocardial infarction, dysrhythmias, endocarditis, and dissection of the aorta (Lange and Hillis 2001).

Fortunately for most stimulants, the duration of the sympathomimetic effects is short (few hours), and the stimulant-induced rise in BP moves back toward normal within a few hours. Treatment is generally supportive and aimed at reducing the amount of agitation and anxiety with benzodiazepines. In occasional cases, hypertension can be associated with life-threatening complications (e.g., aortic dissection, seizures, stroke, and acute myocardial failure) making pharmacologic treatment of the hypertension justified. There is no definitive accepted strategy for the treatment of stimulant-induced hypertension, and a variety of agents have been described including benzodiazepines and other GABA-active agents, calcium channel blockers, nitric oxide-mediated vasodilators (nitroglycerine), alpha-adrenergic blocking drugs, alpha-2-adrenoreceptor agonists, beta and beta/alpha blockers, and other agents (Richards et al. 2016). The American Heart Association recommends benzodiazepines and nitroglycerine for patients with hypertension and acute coronary symptoms (McCord et al. 2008). While the topic remains controversial, many clinicians advocate avoiding all beta-blockers in stimulant-induced hypertension due to the idea that unopposed alpha-stimulation may paradoxically increase blood pressure. The theory proposes that the increasing levels of monoamines induced by cocaine activate alpha-1 adrenoreceptors causing arterial constriction, while the nonspecific beta-



blockade inhibits the compensatory beta-2-mediated vasodilation (Schurr et al. 2014). Despite this concern, many clinicians continue to use beta-blockers for cocaine-related cardiovascular events with few reports of worsening BP or an adverse effect on outcome (Fanari et al. 2014; Richards et al. 2016). More recent literature describes the possible application of dexmedetomidine, an alpha-2 adrenergic receptor agonist, in the treatment of cocaine-induced sympathomimetic actions. In low doses, dexmedetomidine decreases the cocaine-induced rise in blood pressure. However, at higher doses, dexmedetomidine is associated with a paradoxical increase in BP (Kontak et al. 2013), and its application in clinical practice remains untested.

Caffeine is the most widely consumed active pharmacologic substance in the world and is commonly consumed by children thru the intake of coffee, soft drinks, and energy drinks (Branum et al. 2014). While the components of energy drinks often include other additives such as ginseng, guarana, taurine, l-carnitine, and sugars, among others, caffeine is usually the most abundant active ingredient with a caffeine content around 70–80 mg/8 ounces. The caffeine content of energy drinks varies with product and volume and can be as high as 400 mg of caffeine. A typical cola contains 25 mg/8 ounces, tea 50 mg/8 ounces, and coffee 100 mg/8 ounces (Seifert et al. 2011). In a group of young adults a 16 ounce energy drink (240 mg caffeine) increased systolic BP and diastolic BP around 7% from baseline and was significantly higher than the BP response noted in the placebo arm (Svatikova et al. 2015). Caffeine increases BP by increasing the sympathetic activity and antagonism of endogenous adenosine (Nehlig et al. 1992). In habitual coffee drinkers, the average increase in BP following a dose of caffeine is around 1–4 mmHg (Rakic et al. 1999; Jee et al. 1999; Noordzij et al. 2005), but in those infrequently exposed (i.e., children) the blood pressure rise may be as high as 10 mmHg. The effects of caffeine on blood pressure are usually observed for 4–5 h post ingestion (Rakic et al. 1999).

While the inappropriate use of legally prescribed stimulants (e.g., Ritalin) can cause a

significant rise in BP similar to other stimulants, the doses used in the clinical treatment of ADHD result in only mild blood pressure increases. With active treatment, the average increase in SBP and DBP is around 3–4 mmHg (Samuels et al. 2006).

## Club Drugs

Some of the “club drugs,” specifically 3,4-methylenedioxymethamphetamine (MDMA), also known as ecstasy, gamma-hydroxybutyrate (GHB), and ketamine, have been associated with hypertension. Club drug is a generic term for psychoactive drugs used at dance clubs to enhance social interaction and a sense of euphoria and closeness. Of the club drugs, MDMA is most frequently associated with hypertension. MDMA is structurally similar to both amphetamines and the hallucinogen mescaline. MDMA induces a release of serotonin, dopamine, and norepinephrine from the presynaptic neurons and prevents their metabolism by inhibiting monoamine oxidase (Bexis and Docherty 2006). Interestingly, there have been a few randomized placebo studies investigating the physiologic effects of MDMA in adults (De La Torre et al. n.d.; Gouzoulis et al. 1993; Vollenweider et al. 1998). Recreational doses of MDMA (50–150 mg) cause a significant and dose-dependent increase in systolic BP ranging from 10–40 to 5–20 mmHg for diastolic BP. The peak effect on BP occurs in 1–2 h, and the BP returns to normal within 8 h. There are a few cases of accidental MDMA ingestion in young children causing hypertension (Russell et al. 1992; Melian et al. 2004; van Rijswijk et al. 2006; Cooper and Egleston 1997). Although the same concern for the potential of a paradoxical increase in blood pressure has been voiced with the use of beta-blockers in MDMA exposure, carvedilol has been tested and does reduce the increased BP caused by MDMA (Hysek et al. 2012). GHB is a derivative of the inhibitory neurotransmitter gamma-aminobutyric acid. GHB produces euphoria and with chronic use physical and psychological dependence. Although hypertension is not noted with the use of GHB, it is

associated with a GHB withdrawal complex (McDaniel and Miotto 2011) probably due to the excessive central nervous system excitability and adrenergic discharge associated with withdrawal.

## Dissociatives

Ketamine is a derivative of phencyclidine (PCP) and is used clinically as a dissociative anesthetic. When used recreationally, ketamine produces a dreamlike state and visual hallucinations and is also used as a club drug. Ketamine inhibits the neural uptake of norepinephrine, dopamine, serotonin, and glutamate and is associated with the development of hypertension both in clinical use and recreational use (Zielmann et al. 1997; Freese et al. 2002).

PCP was originally used as a powerful animal anesthetic thus the street eponyms of horse tranquilizer and elephant. PCP inhibits serotonin, dopamine, and norepinephrine uptake and increases dopamine and norepinephrine production through stimulation of tyrosine kinase (Bey and Patel 2007). PCP stimulates the sympathetic nervous system and is associated with hypertension (Bey and Patel 2007; Bayorth et al. 1984). The few case reports of PCP in children suggest that hypertension may not be as significant as noted in the adult population (Schwartz and Einhorn 1986; Karp et al. 1980; Welch and Correa 1980).

## Hallucinogens

Lysergic acid diethylamide (LSD), originally introduced as a drug for psychiatric use, is recreationally used for its hallucinogenic effects. Its mechanism of action is incompletely understood but in part acts as a partial/full agonist of the serotonin (5-HT) receptor. Exposure to LSD can cause mild hypertension by unknown mechanisms (Savage 1952). LSD may contain adulterants such as PCP, cocaine, and caffeine that can raise blood pressure independent of LSD. Like most recreational drugs, the half-life is relatively short (5 h), and it is unlikely that specific treatment for the hypertension is needed. Usually

treatment is supportive care and may include benzodiazepines to treat the agitation and anxiety.

Mescaline is another hallucinogenic substance derived from the cactus peyote. Hypertension can be observed with higher doses of mescaline, and it is likely due to the similarity of mescaline to other natural endogenous compound such as dopamine and norepinephrine that leads to CNS stimulation and sympathetic effects. Treatment is supportive.

## Miscellaneous

Anabolic steroids are synthetic substances related to the male sex hormone, testosterone. Although anabolic steroids have been used to treat medical diseases (e.g., muscular dystrophy, aplastic anemia), they are illegally used by male and female athletes for their ability to increase muscle mass and improve performance. The use of anabolic steroids is associated with a host of adverse effects including hypertension (Grace et al. 2003). The presumed mechanism of action is increased salt and water retention but is likely more complex and multifactorial. Unlike other recreational drugs, the duration of action for anabolic steroids may be months.

Chronic alcohol consumption ( $\geq 3$  drinks/day) is associated with an increased incidence of hypertension (Clark 1985). In contrast, mild to moderate alcohol consumption appears to be beneficial to the cardiovascular system and seems to lower blood pressure (Rimm et al. 1996). The average increase in blood pressure in heavy drinkers is 5–10 mmHg. The mechanism by which alcohol causes an increase in blood pressure is unclear, and numerous mechanisms have been forwarded. In hypertension associated with heavy alcohol intake, decreasing the alcohol intake and exercise effectively improve blood pressure (Husain et al. 2014).

In acute settings, nicotine by all routes of administration produces increased blood pressure via stimulation of sympathetic ganglia, the adrenal medulla, and chemoreceptors of the aortic and carotid bodies. Habitual smokers appear to have a lower blood pressure than nonsmokers (Papathanasiou et al. 2016). The blood pressure

lowering may be related to decreases in body weight and to the vasodilatory properties of the nicotine metabolite cotinine (Benowitz and Sharp 1989). Although the overall BP pattern may be improved, smoking causes a transient rise in BP that is present for less than 1 h.

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## Conclusion

In most children elevated blood pressure measurements are transient and due to situational anxiety. When the blood pressure elevations persist, most children are found not to have an identifiable cause for the hypertension. In the minority of children, hypertension is due to an identifiable cause which may include a variety of medications and illicit substances. Substance-induced hypertension can be associated with unexpected and severe blood pressure elevations and should be considered in such circumstances. Fortunately, the blood pressure typically returns to normal values soon after stopping the offending agent, and usually pharmacologic intervention is not required.

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## Cross-References

- ▶ [Diagnostic Evaluation of Pediatric Hypertension](#)
- ▶ [Management of Hypertensive Emergencies](#)
- ▶ [Secondary Forms of Hypertension in Children: Overview](#)

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## Abstract

Hypertension is common in children with cancer, especially among those receiving a hematopoietic stem cell transplant. Elevations in blood pressure can be related to chemotherapy, total body and abdominal radiation, nephrectomy, corticosteroids, excess fluid and salt intake, and calcineurin inhibitor use. Careful attention to the measurement of blood pressure in children with cancer aids in the diagnosis and management of acute complications such as posterior reversible encephalopathy syndrome and thrombotic microangiopathy. Pediatric cancer survivors are at significant risk for developing diabetes, obesity, chronic kidney disease, and hypertension. Hypertension independently contributes to the high burden of cardiovascular disease and mortality in this population. Evidence is needed on the optimal treatment for children with hypertension and cancer, including the potential benefits of angiotensin-converting enzyme inhibitor

therapy and angiotensin receptor blockers in those with concomitant albuminuria and chronic kidney disease. Decreasing the risk of hypertension and its associated complications will improve the health and survival of children treated for cancer and requires a multidisciplinary approach.

## Keywords

Pediatric hypertension • Pediatric cancer • Hematopoietic stem cell transplant

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## Introduction

Children diagnosed with cancer and those undergoing hematopoietic stem cell transplantation (HSCT) are at high risk of developing both acute elevations in blood pressure and chronic hypertension. Hypertension is significant for this patient population, contributing to the already high burden of cardiovascular disease in long-term cancer survivors (Blaes et al. 2016; Oeffinger et al. 2006; Chow et al. 2015; Lipshultz et al. 2013; Diller et al. 2009). Understanding the diagnostic approach, etiologies, and treatment of hypertension in pediatric oncology patients is therefore important to prevent acute complications and decrease future morbidity and mortality from cardiovascular disease.

Multiple providers are involved in the short- and long-term management of children with cancer, including oncologists, pediatricians, transplant specialists, cardiologists, endocrinologists, neurologists, critical care specialists, and nephrologists. It is likely that all of these providers will encounter children with elevated blood pressures during the course of treatment. The goal of this chapter is to summarize the existing literature on the diagnostic evaluation of the child with cancer and elevated blood pressure, the causes of hypertension most relevant to the oncology and HSCT patient, and treatment options that can be tailored to this high-risk population. We focus on studies examining hypertension specifically in children with cancer, but also apply research and guidelines from general pediatric nephrology.

## Definitions

There are currently no definitions of hypertension specific to the pediatric oncology or HSCT population. This is most relevant to the acute outpatient, emergency department, and inpatient settings where these patients are commonly found to have elevated blood pressures on single measurements.

In clinical practice, normative values obtained from healthy children are used to define hypertension in both acute and chronic settings. Normal blood pressure values can be found in the recently issued pediatric hypertension guidelines from the American Academy of Pediatrics (Flynn et al. 2017). Using these consensus guidelines, hypertension is defined as an average systolic or diastolic blood pressure  $\geq 95$ th percentile for a child's age, gender, and height, or  $> 130/80$  in adolescents  $> 13$  years old, on  $\geq 3$  separate occasions. A normal blood pressure is  $< 90$ th percentile. Elevated blood pressure is defined as a blood pressure between these cut-points.

Blood pressure normative values are based on casual measurements, obtained in a clinical setting with either an automated or manual device. Especially in the outpatient setting, these casual measurements may not accurately reflect the blood pressure that a patient is experiencing over the course of their typical day. Therefore, ambulatory blood pressure monitors (ABPM) are increasingly being used to assess a patient's blood pressure load over a 24-h period. Using these methods, white-coat hypertension can be defined as an elevated casual blood pressure but a normal ABPM study, while masked hypertension is defined as a normal casual blood pressure but an elevated 24-h ABPM study. To date, no studies have examined the efficacy of ABPM in the pediatric oncology or HSCT population.

Cancer and HSCT patients may also present with more severe blood pressure elevations, particularly in the emergency department or intensive care unit setting. Hypertensive urgency refers to elevated blood pressures that result in clinical symptoms such as headaches, chest pain, or blurry vision. Hypertensive emergency refers to elevated

blood pressures that result in end-organ damage, such as heart failure. The interested reader is referred to ► [Chap. 45, “Management of Hypertensive Emergencies,”](#) for a thorough discussion of these more severe presentations.

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## Evaluation of Elevated Blood Pressure

### Measurement

It is important to comprehensively evaluate all patients with concern for elevated blood pressure to make sure the readings are not spurious and underlying, potentially modifiable, causes of hypertension are not missed. The assessment of the oncology patient with elevated blood pressure therefore starts with an accurate measurement (see also ► [Chap. 13, “Methodology of Casual Blood Pressure Measurement”](#)). Prior to measurement, children should be sitting calmly for 5 min with their feet on the floor. Blood pressure should be measured in an upper extremity with a cuff that is not too tight and not too loose and covers most of the circumference of the arm. Elevations in blood pressure detected by automatic oscillometric devices, commonly used in the inpatient and outpatient hospital setting, should be confirmed by manual measurements (Flynn et al. 2017; National High Blood Pressure Education Program Working Group on High Blood Pressure in and Adolescents 2004). In critically ill children with arterial pressure measurements, it is important to examine the shape of the arterial waveform and compare the reported values with cuff measurements.

Commonly encountered causes of falsely elevated or spurious blood pressure readings include a cuff that is too small or too tight; measurement during acute pain or after emesis, agitation, or activity; measurement in a lower extremity; or a distorted arterial line waveform. Pain is a common finding in the hospitalized oncology patient, especially from graft-versus-host disease (GVHD) after HSCT, and should be treated before concluding hypertension is actually present. Population normative blood pressure values are based on upper extremity

measurements. However, although upper extremity measurements are preferred, they may not always be possible to obtain in the child with cancer due to the presence of intravenous lines, skin breakdown from GVHD, or patient comfort, especially in the smallest children. In the cases where only lower extremity blood pressures can be obtained, the results should be interpreted in the context of the clinical condition and repeated measurements.

### Clinical History

In the oncology patient with confirmed elevations in blood pressure, a thorough history and physical examination can evaluate the cause and plan for appropriate treatment. Symptoms of elevated blood pressure in children include headaches, blurry vision, chest pain, and nosebleeds. In younger children who are less likely to verbalize these symptoms, signs of hypertension can include abdominal pain, vomiting, and agitation. Symptoms of hypertension can often be difficult to interpret, especially in the acute setting, as many can cause or be the effect of elevated blood pressures. A history of blood or dark colored urine can suggest a renal etiology for elevated blood pressure. Patients should also be asked about any swelling of the eyes or ankles suggesting fluid overload from cardiac disease, renal dysfunction, or low albumin states.

A careful review of all medications and supplements that a patient is taking is critical in the evaluation of the oncology patient with hypertension. A summary of the most common agents associated with elevations in blood pressure in children treated for cancer or receiving a HSCT is shown in [Table 1](#). Briefly, chemotherapeutic agents associated with elevated blood pressures include vascular endothelial growth factor inhibitors, cyclophosphamide, and ifosfamide. Erythropoietin-stimulating agents can cause elevated blood pressure by increasing blood viscosity and altering vascular smooth muscle function. Calcineurin inhibitors used for the prevention and treatment of GVHD after HSCT are associated with significant renal arteriolar vasoconstriction and hypertension,



**Table 1** Medications commonly associated with causing elevated blood pressure in children treated for cancer

Medication class	Indications for use in children treated for cancer or with hematopoietic stem cell transplant	Specific agents	Mechanisms of inducing high blood pressure
Calcineurin inhibitors	Graft-versus-host disease prophylaxis or treatment	Cyclosporine Tacrolimus	Renal arteriolar vasoconstriction
Vascular endothelial growth factor (VEGF) inhibitors/angiogenesis inhibitors	Decrease mortality in certain types of cancer	Sorafenib Sunitinib Bevacizumab	Vasoconstriction by decreased production of nitric oxide
Alkylating agents	Chemotherapy, alone or as conditioning for hematopoietic stem cell transplant	Cyclophosphamide Ifosfamide	Endothelial damage Chronic kidney disease
Radiation	Alone or as conditioning for hematopoietic stem cell transplant	Total body irradiation Abdominal radiation	Endothelial damage Thrombotic microangiopathy Chronic kidney disease
Corticosteroids	Chemotherapy Graft-versus-host disease prophylaxis or treatment	Prednisone Methylprednisolone Hydrocortisone	Sodium retention Increased blood volume Increased vascular tone
Erythrocyte stimulating agents	Anemia secondary to cancer or chronic kidney disease	Erythropoietin Darbepoetin	Increased hematocrit Vascular smooth muscle disruption

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especially when drug concentrations are supra-therapeutic. Corticosteroids are commonly prescribed to children with cancer and lead to elevated blood pressures by promoting salt retention (*Abi Aad et al. 2015; Maitland et al. 2010; Mouhayar and Salahudeen 2011*).

In reference to sodium chloride intake, patients with hypertension need a detailed assessment of their salt intake through their oral diet, intravenous fluids, and parenteral nutrition composition. It cannot be overemphasized that simply decreasing the fluid and salt intake for patients with hypertension can lead to rapid and significant improvements in blood pressures. Other medications commonly prescribed to children with cancer that can be related to hypertension include thyroid supplementation and existing antihypertensive therapy. Hypo- or hyperthyroidism can be associated with hypertension. In patients prescribed clonidine for sedation or hypertension, abrupt withdrawal of the medication can lead to rebound hypertension. For patients receiving transdermal clonidine, making sure the patch is on the skin and changed every 7 days is crucial.

## Physical Examination

The physical examination of oncology patients with hypertension should start with an assessment of the vital signs, with a focus on the heart rate and weight. Bradycardia and hypertension may be associated with central nervous system lesions. Tachycardia and hypertension may be a sign of catecholamine excess from pheochromocytoma or neuroblastoma. Four extremity blood pressures and assessment of peripheral pulses are important to rule out coarctation of the aorta. Examining trends in the patient's weight is very important to assess for fluid overload from salt retention or kidney dysfunction. It is common for patients to acutely gain considerable weight secondary to fluid overload during acute oncology treatment from high rates of intravenous fluids needed to maintain hydration during chemotherapy and corticosteroid use leading to salt retention. Accordingly, the examination of children with elevated blood pressure should focus on edema assessments of the eyes, sacrum, and lower extremities. Abdominal examination is important to detect

renal bruit and masses that could be associated with Wilms tumor or neuroblastoma. A careful neurological examination is important to rule out central nervous system disease as a cause or consequence of hypertension.

### Laboratory Evaluation

All oncology patients with hypertension should have a routine urinalysis looking for proteinuria and hematuria to screen for kidney disease. The urine specific gravity can help in the determination of a patient's hydration status. For example, a concentrated urine with a specific gravity  $>1.020$  can be associated with volume depletion. Measuring electrolyte concentrations is also critical in children with cancer presenting with hypertension. Hyponatremia can be a sign of fluid overload, while in rare cases, hypernatremia can be a sign of salt intoxication, although hypernatremia typically reflects free water deficits. Hypokalemia can be associated with renin excess. The serum albumin level is important for diagnosing nephrotic syndrome or protein losing enteropathy as causes of fluid overload. A complete blood count with differential is important for diagnosing thrombotic microangiopathy, looking for anemia, thrombocytopenia, and the presence of schistocytes. Other markers of hemolysis include an elevated lactate dehydrogenase and a low haptoglobin, which should be checked if there are clinical concerns for hemolysis. Second-line laboratory assessments include thyroid function studies and urine and plasma catecholamine levels, as indicated.

### Imaging

Imaging studies are important in the evaluation of patients with hypertension who are undergoing treatment for cancer. It is important to determine the patient's renal anatomy, either by reviewing a prior CT scan or MRI or ordering a renal ultrasound. The goal is to determine that the patient has two kidneys, and to assess the renal size, look for hydronephrosis, and make sure there are no extrarenal masses or tumors compressing the

kidney. This information can be obtained with the use of a routine renal/bladder ultrasound examination. Doppler examination is not typically needed, especially because it often misses small vessel obstruction. In patients with concern for external vascular compression by mass, venous thrombus, or arterial obstruction, Doppler examination by ultrasound and CT angiography are the preferred methods of evaluation. Central nervous system imaging should be strongly considered in the patient presenting with seizures, hypertension, bradycardia, unexplained vomiting, or altered mental status. Finally, in patients with concern for more chronic hypertension, echocardiography looking for qualitative signs of left ventricular hypertrophy or elevations in measured left ventricular mass can be very useful.

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### Hypertension Associated with Specific Cancer Diagnoses

Any patient undergoing treatment for cancer is at high risk of developing hypertension due to the chemotherapy and radiation they receive (Abi Aad et al. 2015; Mouhayar and Salahudeen 2011). However, in children, certain diagnoses such as neuroblastoma, Wilms tumor, and pheochromocytoma are commonly associated with acute elevations in blood pressure during presentation and the early course of therapy. For Wilms tumor and neuroblastoma, the use of abdominal radiation is a particularly important risk factor for the later development of hypertension (Lipshultz et al. 2013).

Wilms tumor is the fifth most common cancer most common cancer in children and is treated with a combination of surgery, chemotherapy, and radiation depending on the underlying stage and histology (Interiano et al. 2015). Although current survival for patients with Wilms tumor is  $>90\%$ , there is a subset of patients with unfavorable histology or bilateral disease that are at higher risk for worse outcomes. In an effort to decrease long-term complications in children surviving Wilms tumor, newer protocols attempt to minimize exposure to radiation therapy and chemotherapy, as possible (Dome et al. 2015). Children presenting with a renal mass are at increased risk for acute elevations

in blood pressure, and long-term survivors are at higher risk for chronic kidney disease, proteinuria, and hypertension (Interiano et al. 2015).

In the acute setting, blood pressure management is often required prior to surgery, and most children with Wilms tumor will normalize their blood pressure after surgery. Maas et al. conducted a retrospective study of 86 children diagnosed with Wilms tumor who were treated with chemotherapy and surgery. About half of the patients presented with hypertension and elevated levels of renin were found in 25/31 hypertensive children who were assessed. More than 90% of patients had their blood pressure return to normal after surgery, supporting that the acute increases in blood pressure were either from primary secretion of renin by the tumor or secondary to compression of healthy kidney tissue by the mass (Maas et al. 2007). This has supported some to use angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) in the treatment of acute hypertension in children with Wilms tumor (Wong and Mauger 2004). Other reported mechanisms of hypertension in children diagnosed with Wilms tumor include venous thrombosis and obstruction (Madre et al. 2006).

The surgical treatment for Wilms tumor depends on whether one or both kidneys are affected and the histology of the tumor. In patients with unilateral disease, treatment includes unilateral nephrectomy. Using this approach, hypertension has been reported to develop in 7% of survivors after a median of almost 20 years of follow-up (Interiano et al. 2015). In patients with Wilms tumor affecting both kidneys, bilateral nephron-sparing surgery was associated with a lower risk of hypertension compared to patients who received a unilateral nephrectomy combined with contralateral partial nephrectomy (Hubertus et al. 2015). Among patients with favorable histology bilateral Wilms tumor, bilateral nephron-sparing surgery has been associated with normal kidney function but a 25% risk of hypertension (Kieran et al. 2014).

Neuroblastoma is another tumor that can be frequently associated with hypertension. Neuroblastoma is the most common extracranial solid tumor in children, and tumors are derived from the adrenal neural crest cells that secrete

catecholamines (Seefelder et al. 2005). Among children diagnosed with neuroblastoma, 10–30% will have elevated blood pressures on presentation, likely secondary to catecholamine secretion by the tumor. Some patients do not have hypertension despite very high blood catecholamine concentrations, and it is believed that chemotherapy can trigger elevated blood pressures in these patients due to tumor lysis (Kwok et al. 2014; Seefelder et al. 2005). Similar to patients with pheochromocytoma, careful attention to anesthesia management is important in patients with neuroblastoma and hypertension to prevent elevated intraoperative blood pressures secondary to catecholamine surges. As detailed in the information below on pheochromocytoma, patients with concern for catecholamine excess should be treated with alpha-adrenergic blockade prior to receiving any kind of beta-blockade.

Treatment for neuroblastoma includes chemotherapy, radiation, and HSCT for higher-stage diseases. Iodine-labeled metaiodobenzylguanidine (MIBG) is a targeted therapy for children with neuroblastoma because MIBG is an analogue of norepinephrine that is taken up by neuroblastoma cells. Wong et al. reviewed 172 patients receiving 218 MIBG treatments at a single center over a 13-year period. They found that 51% of treatments were associated with systolic hypertension, although most of these episodes resolved after a few days (Wong and Mauger 2004).

Finally, children diagnosed with pheochromocytoma are a unique population with a high risk for hypertension. However, most pheochromocytomas are benign with symptoms resolving after tumor resection, with malignant disease being very rare. It is now reported that 40% of patients with pheochromocytoma have a genetic syndrome including mutations in succinate dehydrogenase, multiple endocrine neoplasia type 2, Von Hippel-Lindau syndrome, and neurofibromatosis. An excellent review on the diagnosis and management of children with pheochromocytoma is summarized below (Havekes et al. 2009). Further information can be found in ► [Chap. 29, “Endocrine Hypertension.”](#)

Pheochromocytoma are tumors derived from the adrenal medulla or extra-adrenal paraganglionic tissue. The average age of presentation is 11 years and children present with hypertension in 60–90%

of cases. In pediatric patients with persistent hypertension of unknown etiology, it has been estimated that 1% will have a pheochromocytoma. The hypertension in patients with pheochromocytoma can be variable (with many patients not having hypertension) and intermittent (with 24-h ambulatory blood pressure studies not showing persistent hypertension and some patients even experiencing hypotension). Symptoms of catecholamine excess may require a high index of suspicion to detect and include palpitations, headache, diaphoresis, pallor, nausea, vomiting, weight loss, polyuria, vision changes, anxiety, flushing, and behavioral changes similar to attention deficit hyperactivity disorder (Havekes et al. 2009).

To diagnose pheochromocytoma, patients should have supine testing for plasma-free normetanephrine and metanephrine with or without 24-h urine testing for fractionated metanephrines. Testing can be falsely influenced by concomitant use of tricyclic antidepressants, beta-blockers, calcium antagonists, and acetaminophen. If pheochromocytoma is suspected based on laboratory studies, imaging with MRI and MIBG scans should be used to locate the tumor. Prior to removing the tumor, catecholamines should be blocked for 10–14 days before surgery. Alpha blockade is the mainstay of treatment with either the noncompetitive antagonist phenoxybenzamine or the competitive agonist doxazosin. The benefits of noncompetitive inhibition are the decreased risk of displacing the receptor antagonist by intraoperative catecholamine surges, but the disadvantage is a higher risk of postoperative hypotension. Calcium channel blockers can be used as adjuvant therapy but beta-blockers should be avoided until alpha blockade is adequate. Ideal blood pressure management for adults prior to surgery includes sitting blood pressure <130/80 mmHg and a standing blood pressure >100 mmHg with a normal heart. In children, the preoperative goal should be a normal blood pressure for age, gender, and height with the presence of an orthostatic drop. During and before surgery, careful consideration should be made to a patient's fluid status, as volume depletion is common in these patients, potassium, and glucose levels given the rapid changes in catecholamine concentrations (Havekes et al. 2009).

## Syndromes of Acute Hypertension in the Pediatric Oncology Patient

Acute elevations in blood pressure can cause symptoms such as headaches, abdominal pain, and visual changes. Severe, acute hypertension in patients with cancer can result in end-organ damage to the central nervous system (posterior reversible encephalopathy syndrome or PRES) and kidney (thrombotic microangiopathy or TMA). In these clinical situations, which are detailed in this section, it is often difficult or impossible to determine if the hypertension is the cause – or the effect – of the acute organ dysfunction.

### Posterior Reversible Encephalopathy Syndrome (PRES)

PRES was first described in 1996 as reversible, radiographic findings of edema of the posterior brain, without infarction, associated with headache, seizures, visual disturbances, and altered mental status (Hinchey et al. 1996). Relatively large case series have reported that while posterior brain abnormalities are most commonly reported in children with PRES, imaging studies have also shown involvement of the frontal, parietal, and temporal lobes (Khan et al. 2016; Tambasco et al. 2016).

Masetti et al. comprehensively reviewed the literature on the pathophysiology, clinical presentation, and treatment of PRES in children receiving an HSCT or solid organ transplant (Masetti et al. 2015). They reported that in children receiving immunosuppression for a solid organ or HSCT, the incidence of PRES is 1–10%. PRES has also been reported in children with cancer who have not received an HSCT. The authors summarized two different theories as to the cause of PRES. In the first, hypertension causes PRES through *cerebral hyperperfusion* and edema when the brain's autoregulatory system becomes overwhelmed by high blood pressure. In the second theory, hypertension is a result of PRES after endothelial injury in the context of transplantation causes *cerebral hypoperfusion*, leading to hypertension to maintain blood flow to the brain. Evidence for the hyperperfusion theory includes the

temporal association between PRES and hypertension and the high risk of elevated blood pressures in the acute transplant setting. Evidence of the hypoperfusion theory includes the fact that up to a third of patients with PRES do not have very high blood pressures, neuroimaging and autopsy studies have shown evidence of decreased blood flow, and endothelial injury is very common from GVHD, bacterial and viral infections, and calcineurin inhibitors (Masetti et al. 2015; Appachu et al. 2014; Tambasco et al. 2016).

The role of magnesium in the pathophysiology of PRES has gained interest. The calcineurin inhibitors tacrolimus and cyclosporine, commonly used to prevent GVHD after HSCT, are known to cause hypomagnesemia. Supporting the cerebral hyperperfusion theory of PRES, magnesium vasodilates cerebral blood vessels which protects the blood-brain barrier. Therefore, children with hypomagnesemia may be more susceptible to the effects of systemic hypertension on the cerebral vasculature. It is interesting to note that the immunosuppressive medication sirolimus, which does not cause hypomagnesemia, has been less frequently associated with the development of PRES (Masetti et al. 2015). In some series, hypomagnesemia was present during acute symptoms of PRES (Khan et al. 2016), while in others all patients had normal magnesium levels (Morris et al. 2007).

Although transplantation is a risk factor for PRES, several reports have included children with cancer who were diagnosed with PRES who had not received an HSCT and therefore were not exposed to calcineurin inhibitors. Khan et al. reviewed the records of over 5000 children treated at St. Jude Children's Research Hospital over a 14-year period and found PRES was diagnosed in 37 patients, with about half developing PRES after HSCT. The incidence of PRES was significantly higher in those with an underlying diagnosis of leukemia (1.6%) when compared to patients with a brain (0.3%) or other solid tumor (0.4%). Almost all of the patients in their cohort had hypertension and corticosteroid use was a presumed risk factor (Khan et al. 2016). In children with acute lymphoblastic leukemia, corticosteroids have been associated with the development of

PRES, especially when used as a component of induction chemotherapy protocols including vincristine, doxorubicin, L-asparaginase, and intrathecal methotrexate (Appachu et al. 2014; Tang et al. 2016).

Given that "reversibility" is one of the hallmarks of PRES, symptoms typically resolve without long-term complications and recurrence of PRES is very rare. However, there are reports of cerebral hemorrhage, herniation, and death related to the diagnosis of PRES in children with cancer (Masetti et al. 2015; Tambasco et al. 2016). Long-term neurologic sequelae of PRES include neurological motor deficits and the need for chronic antiepileptic therapy in <20% (Khan et al. 2016; Tambasco et al. 2016). Until there is a better understanding of the mechanisms leading to PRES and the most important risk factors, prevention and treatment of PRES remains supportive with careful monitoring and treatment of hypertension and levels of immunosuppressive medications, maintaining normal electrolytes, and treating seizures in collaboration with critical care and pediatric neurology teams (Masetti et al. 2015; Tambasco et al. 2016).

### **Thrombotic Microangiopathy**

TMA is defined as characteristic endothelial damage of small vessels on tissue pathology (Laskin et al. 2011a; Batts and Lazarus 2007). While the kidney is the most commonly affected organ, TMA can be associated with injury to the heart, lungs, brain, and gastrointestinal tract (Jodele et al. 2015). The clinical findings of TMA include hemolytic anemia presenting with an elevated lactate dehydrogenase, low haptoglobin, anemia, and thrombocytopenia. Renal manifestations include acute kidney injury, proteinuria, and hypertension, which can progress to chronic kidney disease (Laskin et al. 2011b). Extrarenal signs and symptoms of TMA are polyserositis, pericarditis, heart failure, pulmonary hypertension, seizures, and gastrointestinal bleeding that often mimics GVHD (Dandoy et al. 2013; El-Bietar et al. 2015; Lerner et al. 2014). While the etiology of TMA depends on the population studied, reported risk factors

include viral, bacterial, and fungal infections, use of calcineurin inhibitors, chemotherapy, radiation, GVHD, dysregulation of the clotting cascade, and acquired or inherited abnormalities of the complement pathway (Batts and Lazarus 2007; Laskin et al. 2011a; Hingorani 2016; Jodele et al. 2013, 2014a, 2016b; Kintzel 2001).

In children with cancer, TMA is most commonly reported as a complication of HSCT, but has also been identified in children receiving chemotherapy who have not undergone transplantation. TMA has been reported in children with cancer receiving tyrosine kinase inhibitors (Ruebner et al. 2014). Given the findings of TMA described on biopsy, where damage to small vessels is invariably present, processes that lead to significant endothelial cell damage, including chemotherapy, radiation, and the increasing use of specific agents such as vascular endothelial growth factor inhibitors, have been associated with TMA (Eremina et al. 2008; George and Nester 2014).

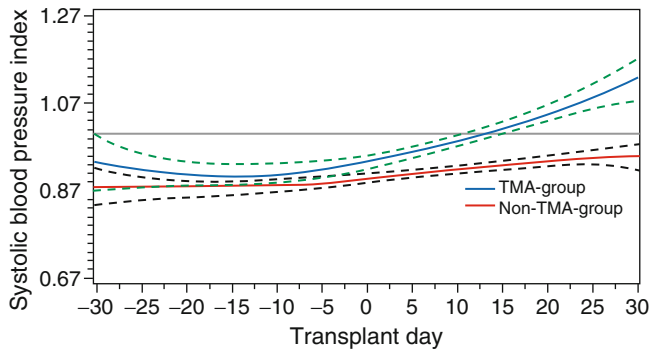
The diagnosis of TMA requires a high index of suspicion, especially in children with cancer, because the findings of anemia, thrombocytopenia, and acute hemolysis are so common in this population. However, it is worth noting that the anemia and thrombocytopenia are often out of proportion to what would be expected in a patient who has bone marrow suppression, especially an increased requirement for red cell and platelet transfusions to maintain blood counts. Careful attention to signs of renal (proteinuria and unexplained increases in blood pressure) and cardiovascular disease (including echocardiogram findings) can also be extremely helpful in detecting TMA (Laskin et al. 2011b; Jodele et al. 2014a; Dandoy et al. 2015).

Hypertension has been shown to be an early indicator of TMA in children with neuroblastoma undergoing autologous HSCT, a population that receives standardized chemotherapy and does not require calcineurin inhibitor therapy for GVHD prophylaxis. In a case-control study including 20 children with neuroblastoma, those eventually developing TMA ( $n = 6$ , 30% prevalence) had statistically higher blood pressures after starting conditioning chemotherapy but 3 days before stem cell infusion compared to the 14 patients who did not develop TMA. Among patients with

TMA, systolic hypertension, defined as blood pressures >95th percentile for age, gender, and height, developed 2 weeks after stem cell infusion and about 1 week before clinical signs of hemolysis were apparent (Fig. 1). These findings suggest that blood pressure abnormalities are an early sign of endothelial injury in children with TMA (Laskin et al. 2011b). Studies in adults have supported the strong associations between TMA and the subsequent development of hypertension in those receiving T-cell-depleted grafts that did not receive calcineurin inhibitor therapy (Glezerman et al. 2010). Because hypertension is so common in the HSCT population, even in the absence of TMA, some have suggested that TMA should be strongly considered in children receiving more than two antihypertensive medications (Jodele et al. 2015; Laskin et al. 2011a).

The etiology of hypertension in patients with TMA is likely related to small vessel injury in the kidney, including renin-mediated increases in blood pressure. With increasing evidence supporting the role of complement dysregulation in the pathogenesis of TMA, we and others have shown increased deposition of the classical pathway degradation product C4d in the kidney of patients with TMA, similar to what is found in patients with antibody-mediated kidney transplant rejection (Laskin et al. 2013; Mii et al. 2011a, b). The presence of C4d in kidney arterioles may be a specific histological marker of TMA, may identify a site of complement-mediated endothelial injury, and may therefore explain why patients with TMA develop hypertension (Chua et al. 2015; Laskin et al. 2013).

Close monitoring of blood pressure in children with cancer, especially those undergoing HSCT, is important for diagnosing TMA at an early and potentially more treatable stage before end-organ damage becomes irreversible (Jodele et al. 2012, 2014b, 2016a). Among patients who develop hypertension in the context of TMA, it is important to prevent acute complications such as PRES and seizures. In those with chronic kidney disease secondary to TMA, treatment of hypertension likely helps to slow the progression of kidney disease. In the only randomized trial to assess a therapy in patients at risk for TMA after HSCT, Cohen et al. randomized 55 patients (3 of whom



**Fig. 1** Hypertension as an early marker of thrombotic microangiopathy (TMA) in 20 children with neuroblastoma. A cubic regression model was used to generate systolic blood pressure index plots over time, in which day  $-7$  is the start of transplant chemotherapy and day  $0$  is stem cell infusion. An index value is the patient's blood pressure divided by their 95th percentile value for age and sex. Systolic blood pressure indices for the TMA group ( $n = 6$ , blue lines) and the non-TMA group ( $n = 14$ , red lines) are plotted with surrounding 95% con-

fidence intervals (dotted lines). Values above the horizontal line (drawn at a blood pressure index  $\geq 1$ ) represent hypertension. Compared with the non-TMA group, average systolic blood pressure levels in the TA-TMA group were significantly higher on day  $-3$  of chemotherapy and thus already before stem cell infusion. Systolic hypertension was apparent by day  $+13$  (about 1 week before the diagnosis of TA-TMA) and persisted despite antihypertensive therapy (Laskin et al. 2011) (Copyright 2010, Rights Managed by Nature Publishing Group, used with permission)

were children) to captopril or placebo starting on the day of engraftment. The primary outcome was the development of bone marrow transplant nephropathy (TMA), defined as a doubling of the baseline serum creatinine, hypertension, and anemia. Patients took study drug for a mean of 2 months, with five subjects in each group completing 1 year of treatment. Although the small sample size precluded statistically significant findings, there were trends favoring the use of captopril (Figs. 2 and 3): patients receiving captopril had  $0.15$  mg/dL lower 1-year creatinine values ( $p = 0.2$ ), an almost  $10$  ml/min/ $1.73$  m<sup>2</sup> ( $p = 0.07$ ) increase in glomerular filtration rate as estimated by the Modification of Diet in Renal Disease formula in adults and nuclear medicine testing in children, and a 20% increase in survival ( $p = 0.09$ ). The incidence of TMA was 3.7% in those receiving captopril and 15% in those treated with placebo ( $p = 0.1$ ) (Cohen et al. 2008).

Similar to what has been shown in children with chronic kidney disease who did not have cancer, ACE inhibitors or ARBs may offer benefit for patients undergoing HSCT, including improvements in blood pressure control, decreases in proteinuria, and slowing the progression of chronic

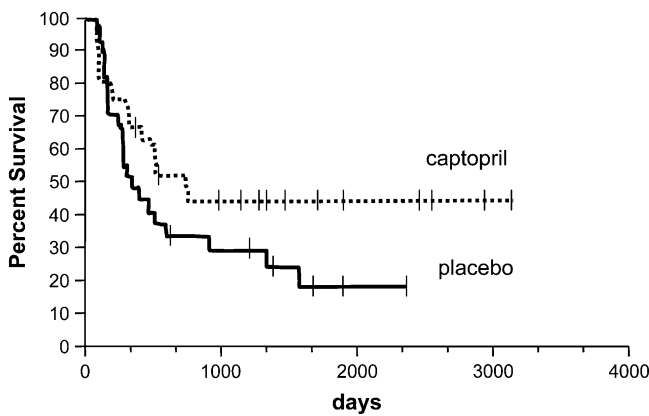
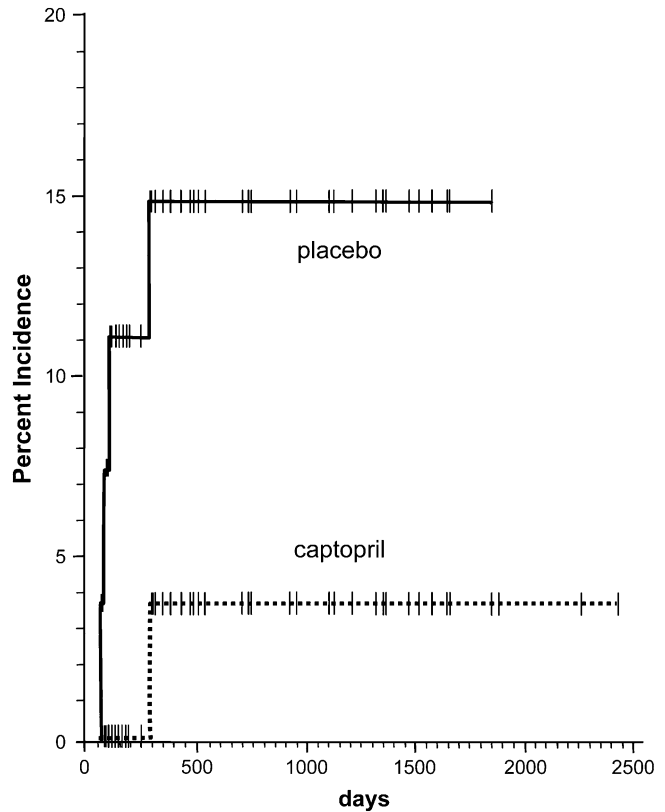
kidney disease (Group et al. 2009). Albuminuria, an early marker of kidney disease and overt proteinuria, is common in patients undergoing HSCT and is associated with poor clinical outcomes (Hingorani et al. 2008; Hingorani 2016). Many providers are appropriately hesitant to prescribe these medications in the acute oncology setting, especially after HSCT, as patients are already at high risk of acute kidney injury and hyperkalemia (Jodele et al. 2015). To date, no trials have been designed in children to test the potential benefits and risks of using agents that target the renin-angiotensin axis in treating albuminuria, TMA, and improving survival in those with cancer.

## Long-Term Elevations in Blood Pressure in Children Treated for Cancer

### Overview of Incidence and Prevalence

Multiple studies have assessed the long-term risk of hypertension in children treated for cancer. These mostly retrospective studies report different risks of hypertension, depending on the age and

**Fig. 2** Incidence of thrombotic microangiopathy in a trial of captopril after stem cell transplant. The cumulative incidence of bone marrow transplant nephropathy and hemolytic uremic syndrome according to the use of captopril or placebo. The placebo group ( $n = 27$ ) and a higher rate than the captopril group ( $n = 28$ ), but this did not attain statistical significance ( $p = 0.1$ ) (Reprinted from Cohen et al. (2008). Copyright (2008), with permission from Elsevier)



**Fig. 3** Survival in those treated with captopril in a trial after stem cell transplant. The actuarial patient survival according to the use of captopril ( $n = 27$ ) or placebo ( $n = 28$ ). There was better patient survival in the subjects in the captopril group, with a possible increasing survival

advantage over time. This survival difference did however not attain statistical significance ( $p = 0.09$ ) (Reprinted from Cohen et al. (2008). Copyright (2008), with permission from Elsevier)

demographics of the study population; the definition of hypertension, using actual blood pressure measurements versus patient-reported disease; the underlying cancer diagnosis; the length of follow-up;

and whether or not a patient received an HSCT. A Cochrane Review of 24 studies found a reported prevalence of hypertension from 0% to 18.2%. Risk factors for long-term hypertension



after treatment for childhood cancer included a higher body mass index, total body irradiation, abdominal irradiation, acute kidney injury, unrelated allogeneic HSCT, autologous HSCT, growth hormone therapy, and older age at follow-up. Only a higher body mass index was associated with hypertension in more than one study's multivariate analysis (Knijnenburg et al. 2013). Unless otherwise specified, the following studies defined hypertension as a blood pressure  $\geq 140/90$  mmHg or receiving medication for treatment in adults and  $>95$ th percentile for age, sex, and height in children.

As mentioned above, the reported prevalence of hypertension in children treated for cancer varies depending on the underlying disease, the definition of hypertension used, whether or not patients received HSCT, and the length of follow-up (Knijnenburg et al. 2013; Ellis et al. 2008). Children with cancer undergoing HSCT may have a higher risk of hypertension due to medications including use of high-dose chemotherapy and total body irradiation as part of the conditioning regimen and corticosteroids and calcineurin inhibitors for prevention and treatment of GVHD.

In one of the few studies prospectively assessing the risk of hypertension in the pediatric oncology population, 11% of 66 children developed hypertension in the first 3 months after HSCT, with 1 out of 42 surviving patients (2%) receiving antihypertensive therapy 1 year after transplant (Kist-van Holthe et al. 2002). The largest retrospective studies examining blood pressure note hypertension in 14.8% of those  $>5$  years after any childhood cancer diagnosis (Knijnenburg et al. 2012), with the prevalence increasing to 36% among those surviving  $>5$  years after receiving an HSCT as a child (Hoffmeister et al. 2010). Others have observed a hypertension prevalence of 23% (Dekkers et al. 2013) at a median of 18 years after childhood cancer diagnosis.

### Long-Term Hypertension in Pediatric Cancer Survivors

In one of the largest studies to date, Meacham et al. reported on 8599 patients in the Childhood

Cancer Survivor Study who survived more than 5 years after cancer diagnosis who were assessed by a patient- and sibling-completed questionnaire (Meacham et al. 2010). Among survivors, 8.8% of patients were currently taking a medication for hypertension compared to 5.7% in their siblings (odds ratio 1.9, 95% confidence interval 1.6–2.2). Risk factors for hypertension included black race, older current age, younger age at diagnosis, higher anthracycline dose, abdominal or chest radiation, decreased physical activity, and current steroid use. Patients with kidney tumors or osteosarcoma had three times the risk of hypertension relative to siblings, while those with Ewing sarcoma, neuroblastoma, lymphoma, and acute myelogenous leukemia had at least double the risk of hypertension compared to their siblings.

Armstrong et al. expanded on these findings to estimate risk factors associated with major cardiac events in the Childhood Cancer Survivor Study. Although this study was also limited by the use of patient questionnaire for identifying hypertension, hypertension was independently associated with a significantly increased risk of coronary artery disease, heart failure, valvular heart disease, arrhythmia, and cardiac death (Armstrong et al. 2013).

Other studies including children with cancer have measured blood pressures at different times after diagnosis to estimate the prevalence of hypertension and associated risk factors. In the largest and most comprehensive such study, Knijnenburg et al. retrospectively reviewed all children who had survived 5 years after a diagnosis of pediatric cancer in Amsterdam, the Netherlands, from 1966 to 2003 and attended a specialized long-term oncology survivorship clinic (Knijnenburg et al. 2012). Of those were alive as of January 1996, 1442 patients were included in the analysis. The median patient age at follow-up was 19.3 years and patients were a median of 12.1 years since their original cancer diagnosis. Of the 1442 total patients, 207 (14.4%) had history of a renal tumor and 96 (6.7%) were previously diagnosed with neuroblastoma. Overall, elevated blood pressure/hypertension was present in 14.8% of survivors; however, this may overestimate the risk of hypertension given that most patients with elevated blood pressures had

single measurements performed in clinic. The authors also reported that female cancer survivors 20–29 years of age and male cancer survivors 30–39 years of age had a two to three times higher risk of elevated blood pressure compared to the general population. Though other age groups also had a higher risk of elevated blood pressure compared to the general population, the risks were not statistically significant. Finally, by multivariable analysis, having received abdominal radiation, an older age at cancer diagnosis, a longer time since diagnosis, and male sex were independently associated with a higher risk of elevated blood pressure at long-term follow-up. When examining cumulative doses of ifosfamide, cisplatin, or carboplatin, high-dose cyclophosphamide or methotrexate, nephrectomy, or total body irradiation, investigators did not find an association between these factors and elevated blood pressure (Knijnenburg et al. 2012).

Several smaller studies, both in the United States and Europe, have estimated the risk of hypertension in long-term survivors of cancer. Chow et al. reviewed 165 children who were diagnosed with acute lymphoblastic leukemia and treated on pediatric cooperative group oncology trials at the Fred Hutchinson Cancer Research Center in Seattle, Washington, from 1993 to 2003. Blood pressure readings were examined 1 month after diagnosis (end of induction), 6 months after diagnosis (beginning of maintenance therapy), and annually thereafter. Systolic and diastolic blood pressure measurements were converted to z-scores using age, sex, and height normal values. Blood pressures were also categorized as pre-hypertension (90–94th percentile or a value  $\geq 120/80$  mmHg) or stage 1 hypertension ( $\geq 95$ th percentile plus 5 mmHg or  $\geq 140/90$  mmHg) (Chow et al. 2007).

At the end of induction therapy, 63.3% of patients had blood pressure values consistent with stage 1 hypertension, a proportion that decreased to 15.3% by the end of therapy. Five years after therapy completion, 14.1% of patients still met stage 1 hypertension criteria, but none were receiving antihypertensive therapy. By multivariate analysis, the highest levels of cumulative steroid exposure ( $\geq 10,000$  mg/m<sup>2</sup>), but not lower

levels, were independently associated with a higher risk of hypertension. Younger age at diagnosis and female sex were also associated with elevated blood pressures. Neither treatment intensity nor having received cranial radiotherapy was associated with changes in blood pressure (Chow et al. 2007).

Esbenshade et al. conducted a retrospective cohort study of 183 children treated for acute lymphoblastic leukemia from 2000 to 2008 at Vanderbilt, Tennessee (Esbenshade et al. 2011). Consistent with guidelines for defining hypertension in the general pediatric population then in place (National High Blood Pressure Education Program Working Group on High Blood Pressure in and Adolescents 2004), pre-hypertension was defined as an average blood pressure  $>90$ th percentile, and hypertension was defined as a measurement  $>95$ th percentile on three or more separate occasions. The median age of the cohort was 5.7 years and patients were followed until 1 year after completing chemotherapy. 16.7% of patients needed antihypertensive medications during chemotherapy with most receiving blood pressure medications only during corticosteroid use. Median systolic blood pressures were elevated from induction through delayed intensification but were normal by the start of maintenance. During the course of follow-up, 31.1% of patients had systolic pre-hypertension and 41.5% of patients had systolic hypertension.

Two European studies, one from the Netherlands (Dekkers et al. 2013) and the other from Finland (Pietila et al. 2005), reported on the risk of hypertension in single centers. Dekkers et al. performed a retrospective cross-sectional study of adults who had survived 5 years after stopping therapy for a pediatric malignancy over a 40-year period (1964–2005) (Dekkers et al. 2013). From their single center in the Netherlands, 763 survivors were examined, including 85 patients (11.1%) who had been diagnosed with a renal tumor and 50 patients (6.6%) diagnosed with neuroblastoma. At the time of blood pressure evaluation, the patients were a median of 26.9 years old and had been followed for a median of 18.3 years since their cancer diagnosis. Overall, hypertension was present in 23.4% of long-term survivors.

Having received abdominal radiation was the only significant risk factor for the later development of hypertension in this cohort. Specifically, of the 47 children who had received abdominal radiation, 43% developed hypertension. Abdominal radiation had primarily been prescribed for patients diagnosed with a renal tumor or neuroblastoma. Renal shielding was not used in patients treated with abdominal radiation or total body irradiation. A history of nephrectomy; treatment with cisplatin, carboplatin, ifosfamide, and cyclophosphamide; and total body irradiation were not associated with an increased risk of hypertension.

Additionally, Pietila et al. reviewed 104 children diagnosed with a brain tumor in Finland from 1983 to 1997. At a median age of 14.4 years and a median of 6 years after treatment, 52 of 80 surviving patients were included in the analysis. At long-term follow-up, 8/52 patients (15.4%) were hypertensive with 3 of these patients taking antihypertensive therapy. Significant risk factors for elevated blood pressure included cisplatin, cranial radiation, the presence of chronic kidney disease, and hypomagnesemia (Pietila et al. 2005).

Finally, Mudi et al. described 130 pediatric cancer survivors who were in remission and had been treated at a single center in South Africa over a 1-year period. Most of the patients had been diagnosed with leukemia or lymphoma, and 20% of the cohort had a diagnosis of a renal tumor. After a median follow-up of 2 years, only one patient (0.8%) had been diagnosed with hypertension (Mudi et al. 2016).

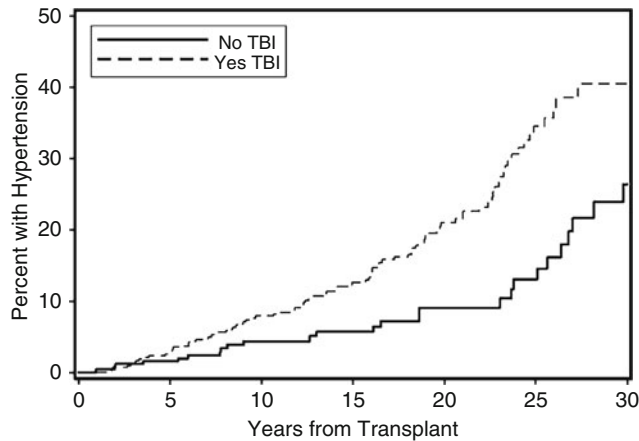
### **Long-Term Hypertension in Pediatric HSCT Survivors**

Several studies have focused on the risk of hypertension specifically in children who survived after receiving an HSCT. In one of the only prospective studies to examine hypertension in children with cancer or undergoing HSCT, Kist-van Holthe et al. followed 66 children after HSCT at Leiden University Medical Center in the Netherlands from 1998 to 2000 and found a lower risk of hypertension than has been reported in retrospective studies (Kist-van Holthe et al. 2002). Blood

pressure measurements were obtained before HSCT, at least four times per day while patients were admitted to the hospital after transplant and 1 year after transplant. Antihypertensive medication was prescribed if repeat blood pressures were  $>10$  mmHg above the 95th percentile for healthy children by age and gender. Prior to transplant, none of the 66 children were taking blood pressure medication or had elevated blood pressures. By 3 months after HSCT, 11% of children required antihypertensive medications, but by 1 year after transplant, only 1/42 surviving patients (2%) was taking antihypertensive medication. In a longer-term follow-up study by the same authors, all children had normal blood pressures 5 years after HSCT (Kist-van Holthe et al. 2005).

The remaining studies examining hypertension in HSCT survivors were retrospective and included mostly small cohorts of patients. In the largest, Hoffmeister et al. reviewed 689 patients who had survived more than 5 years after transplantation at the Fred Hutchinson Cancer Research Center in Seattle, Washington, from 1969 to 2004 (Hoffmeister et al. 2010). For adults, hypertension was defined as a systolic blood pressure  $\geq 140$  mmHg or a diastolic blood pressure  $\geq 90$  mmHg, unless the patient had diabetes, for which a cutoff to define hypertension of  $\geq 130/80$  mmHg was used. Hypertension onset was defined as the first of two consecutive blood pressures reaching the above thresholds or the initiation of medication to treat hypertension. After a median follow-up of 16 years, 17% of the cohort was hypertensive, of whom 65% were being managed with antihypertensive medications. Patients with neuroblastoma had the highest 20-year cumulative incidence of hypertension at 31%. By multivariate analysis, significant, independent risk factors for the development of hypertension included a history of acute kidney injury, total body irradiation, autologous HSCT, unrelated allogeneic HSCT, obesity, and diabetes (Fig. 4). There was a trend toward growth hormone use being an independent risk factor for hypertension.

Three additional, smaller studies reported on the risk of hypertension in pediatric HSCT recipients. Wilhelmsson et al. reviewed 204 pediatric allogeneic HSCT recipients in Finland between 1978 and



**Fig. 4** Risk of hypertension with total body irradiation after pediatric stem cell transplant. Records of 689 pediatric patients who survived 5 years or more after HCT from 1969 to 2004 were reviewed for development of

hypertension. Cumulative incidence of hypertension was higher among those who had received total body irradiation ( $p < 0.01$ ) (Reprinted from Hoffmeister et al. (2010). Copyright (2010), with permission from Elsevier)

2000 who survived more than 4 years after transplant. Hypertension was defined and graded according to the Common Terminology Criteria for Adverse Events and was present in 9.8% of the patients after a median follow-up time of 12 years (Wilhelmsson et al. 2015). Kwon et al. reviewed 157 consecutive children who underwent HSCT in Korea. Blood pressure measurements were obtained at day zero and then weekly until 1 month after transplant. By 1 month after transplant, 38% of patients had been diagnosed with early-onset hypertension during at least one study visit. The risk increases from day 0 (11.2% of patients hypertensive) until day 28 (25.9% of patients hypertensive), with 22.3% of patients noted to be hypertensive at more than two weekly study visits. Patients with hypertension had a longer hospital length of stay. By multivariate logistic regression, older age at transplant was associated with a significantly lower risk of hypertension, and an increase in creatinine from baseline to day 21 was associated with a higher risk of hypertension, independent of acute GVHD, amphotericin exposure, and development of sinusoidal obstruction syndrome of the liver (Kwon et al. 2013).

Finally, Majhail et al. reviewed risk factors for diabetes and hypertension among 106 consecutive adult and 74 consecutive pediatric allogeneic HSCT recipients who had survived more than

1 year after receiving a transplant at the University of Minnesota from 2003 to 2005. During the first 2 years after HSCT, the prevalence of hypertension was similar in children (73%) and adults (68%). Almost 90% of these patients were receiving medication to treat their blood pressure. New-onset hypertension occurred in 61% of patients at a median of 1 month after HSCT. Cyclosporine use was independently associated with the risk of new-onset hypertension during the first 2 years after transplant (Majhail et al. 2009).

## Consensus Recommendations

Several consensus guidelines have been published on recommendations for monitoring blood pressure and treating hypertension in long-term survivors of childhood cancer (summarized in Table 2). Pulsipher et al. summarized a consensus conference organized by the National Heart, Lung, and Blood Institute of the National Institutes of Health called the Pediatric Blood and Marrow Transplantation Consortium First International Consensus Conference on Late Effects after Pediatric Hematopoietic Cell Transplantation. The authors included separate guidelines by the Children's Oncology Group, the United Kingdom Children's Cancer Study Group, and

**Table 2** Summary of consensus guidelines for the screening and treatment of hypertension in children treated for cancer

		At risk	Screening	Treatment
Children's Oncology Group Jones et al. (2008) and Shankar et al. (2008)	<a href="http://www.survivorshipguidelines.org">www.survivorshipguidelines.org</a>	Carboplatin, cisplatin, ifosfamide, methotrexate, abdominal radiation, and total body irradiation, HSCT	Yearly blood pressure check	Nephrology referral for those with hypertension
	Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer. Version 4.0 October 2013.			
	Version 4.0 October 2013.			
UK Children's Cancer Study Group		HSCT	Yearly blood pressure screen	
Adult joint transplant society			Blood pressure assessment at every clinic visit	Aggressive hypertension management
Scottish Intercollegiate Guidelines Network	<a href="http://www.sign.ac.uk">www.sign.ac.uk</a>	Anthracycline treatment	Healthcare professionals should monitor risk factors associated with coronary heart disease such as hypertension	
	Guideline 132: long-term follow-up of survivors of childhood cancer			
NHLBI Pediatric Blood and Marrow Transplantation Consortium			Blood pressure each visit and at least annually, echocardiogram at least every 5 years	ACE inhibitor or ARB if albumin to creatinine ratio is >30 g/kg on 3 occasions in a 6-month period and patient has hypertension

Joint Transplant Society Recommendations including bone marrow transplantation societies from the United States, Asia/Pacific, Europe, Australia/New Zealand, East Mediterranean, and Brazil. The panel recommended screening for hypertension at all long-term HSCT follow-up visits, with careful attention to kidney function (serum creatinine), microalbuminuria, and macroalbuminuria. Hypertension should be aggressively treated in patients after HSCT, especially those who received calcineurin inhibitors. Citing the only randomized controlled trial (Cohen et al. 2008) in adults, reviewed above, the authors speculated whether treatment with an ACE inhibitor or ARB would benefit children with albuminuria and hypertension. Regarding cardiovascular

disease. HSCT recipients are at increased risk for the development of hypertension and diabetes due to total body irradiation, immunosuppression, hypothyroidism, and growth hormone deficiency (Nieder et al. 2011; Pulsipher et al. 2012).

Chow et al. summarized recommendations by the Children's Oncology Group on late effects among children who had received an HSCT. All survivors should be screened for hypertension using age-appropriate criteria to define hypertension. Creatinine and urinalyses should be checked annually starting 1 year after transplantation, and those with hypertension, proteinuria, or chronic kidney disease should be referred to a pediatric nephrologist (Chow et al. 2016). Cardiovascular recommendations included screening for diabetes,

dyslipidemia, hypertension, and tobacco use in survivors treated with anthracyclines, total body irradiation, or chest radiation (Shankar et al. 2008).

Jones et al. summarized recommendations by the Children's Oncology Group for screening for kidney late effects in children treated for cancer in childhood. They suggested that treatments associated with chronic kidney damage and/or later hypertension include cisplatin, carboplatin, ifosfamide, methotrexate, kidney radiation, and nephrectomy. They recommend annual assessment of blood pressure and urine with referral to pediatric nephrology if any abnormalities are detected (Jones et al. 2008).

A collaboration between the Center for International Blood and Marrow Transplant Research and the European Group for Blood and Marrow Transplantation led to recommendations for BP assessment for HSCT recipients at every clinic visit and at least annually (Pulsipher et al. 2012). In adults, they recommend non-pharmacologic treatment for mild hypertension including reduction of sodium intake, weight reduction, avoidance of excess alcohol, and participation in regular exercise (Lipshultz et al. 2013). Treatment is indicated if the blood pressure is  $>140/90$  mmHg on two separate readings at least 1 week apart (Majhail et al. 2012). In children, HSCT-specific guidelines do not exist so a healthy diet, weight, and physical activity are recommended as non-pharmacologic interventions and medications are indicated for stage 2 hypertension or stage 1 hypertension that has not responded to 6 months of lifestyle modification.

Finally, Lipshultz et al. reviewed long-term cardiovascular toxicity in children treated for cancer, creating guidelines from the American Heart Association. Vascular endothelial growth factor receptor inhibitors such as bevacizumab, sorafenib, and sunitinib are associated with increases in blood pressure during the infusion with returns to normal after the infusion was stopped. Evidence is conflicting on the risk of hypertension from ifosfamide, cisplatin, carboplatin, methotrexate, total body irradiation, cranial radiation, chest radiation, or nephrectomy, but annual blood pressure measurements for children exposed to these risk factors seem reasonable. Abdominal radiation, most often for Wilms tumor or neuroblastoma, is

a well-known and consistent risk factor for long-term hypertension (Lipshultz et al. 2013).

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## Treatment

There is little available evidence, particularly in children, to suggest how hypertension should be managed in patients receiving acute or chronic care for malignancy. In the absence of evidence-based guidelines, it seems rational to prescribe antihypertensive medications based on the patient's clinical condition and concomitant medications.

For example, oral or intermittently dosed calcium channel blockers may be a good choice for patients receiving calcineurin inhibitors, as they counteract calcineurin inhibitor-induced vasoconstriction (Abi Aad et al. 2015). However, care must be exercised in patients receiving calcineurin inhibitors and continuous infusions of nicardipine, as patients who are CYP3A5 nonexpressors have been reported to be at increased risk for tacrolimus toxicity while receiving continuous intravenous nicardipine (Hooper et al. 2012). Diuretics, such as furosemide or thiazides, are often a good choice for patients with steroid-induced hypertension from salt and fluid retention. Clonidine can be used as an acute rescue medication or as maintenance therapy in patients with pain or anxiety (Mouhayar and Salahudeen 2011).

In the acute, intensive care setting, continuous infusions of nicardipine, nitroprusside, or esmolol can be helpful to carefully titrate blood pressure control in critically ill children with very close monitoring, especially of calcineurin inhibitor levels, as noted above. Other medications useful for the acute treatment of hypertension in the oncology population include rapidly acting calcium channel blockers such as nicardipine (intravenous) or isradipine (oral), intravenous hydralazine or labetalol, and oral clonidine, captopril, minoxidil, hydralazine, or alpha blockers. Table 3 summarizes commonly used medications in children with cancer and hypertension, including when they should be considered, when they should be avoided, and potential adverse events. Again, as noted in the section on the evaluation of the oncology patient with hypertension, careful

**Table 3** Treatment options for children with hypertension after treatment for cancer

Medication class	When to consider (benefits)	When to avoid (cautions)	Adverse effects
Calcium channel blockers	Calcineurin inhibitor use	Arrhythmias/heart failure without discussion with cardiology	Gingival hypertrophy
	Immobility		Leg edema
	Fractures		
Beta-blockers	Anxiety	Reactive airway disease	Fatigue
	Migraines	Diabetes mellitus	Hyperkalemia
	Tachycardia	Hyperkalemia	Bradycardia
		Bradycardia	
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers	Proteinuria	Hyperkalemia	Cough
	Diabetes mellitus	Acute kidney injury	Angioedema
	Chronic kidney disease	Bilateral renal artery stenosis	Hyperkalemia
	Heart disease		Elevated creatinine
Diuretics	Fluid overload/edema	Hemodynamic instability	Hearing loss
	Salt retention		Electrolyte derangements
	Nephrotic syndrome		Hyper-/hypocalciuria
	Corticosteroid use		
Clonidine	Anxiety	Skin breakdown from GVHD (for patch)	Fatigue
	Pain		Sedation
	Autonomic dysfunction		

attention to a patient's weight, fluid status, sodium intake, steroid exposure, and calcineurin inhibitor level is very important in the prevention and treatment of children with hypertension.

Albuminuria is commonly identified in patients after HSCT and has been associated with worse outcomes (Hingorani et al. 2008). Awaiting confirmatory randomized clinical trials, we suggest that treating children with hypertension and/or proteinuria after a diagnosis of cancer with ACE inhibitors or ARBs may improve chronic kidney disease progression, cardiovascular risk, and survival. As mentioned, a small trial in adults after HSCT supported the potential benefit of captopril (Cohen et al. 2008). In children with chronic kidney disease who were not treated for cancer, the ESCAPE randomized clinical trial showed that targeting blood pressure to <50th with an ACE inhibitor slowed the decline of kidney function

(Group et al. 2009). Similarly designed trials in children with cancer or undergoing HSCT would be helpful to improve outcomes for these high-risk patients.

## Conclusions

Hypertension is common in children treated for cancer and those receiving an HSCT. The exact prevalence of acute elevations in blood pressure and long-term hypertension in this patient population is unknown as few prospective studies have been published. Evidence on the use of 24-h ambulatory blood pressure monitoring in children with cancer would help to better define the specific risk of hypertension and establish the incidence of white-coat and masked hypertension. Total body and abdominal radiation are

consistently reported as risk factors for hypertension. Other potential risk factors include anthracycline, ifosfamide, and cyclophosphamide chemotherapy, nephrectomy, a diagnosis of neuroblastoma or Wilms tumor, and calcineurin inhibitor therapy. Careful attention to blood pressure in oncology patients is important to diagnose and manage acute complications such as PRES and TMA and prevent long-term cardiovascular disease and mortality in this high-risk population. Consensus guidelines support that urinalyses, creatinine, and blood pressure should be checked at least annually in all survivors of pediatric cancer and those undergoing HSCT. Pediatric oncology-specific treatment recommendations for children with cancer and hypertension are needed to determine if ARBs and ACE inhibitors provide benefits by preventing or slowing the progression of chronic kidney disease and improving short- and long-term survival.

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## Cross-References

- ▶ [Cardiovascular Influences on Blood Pressure](#)
- ▶ [Development of Blood Pressure Norms and Definition of Hypertension in Children](#)
- ▶ [Diagnostic Evaluation of Pediatric Hypertension](#)
- ▶ [Endocrine Hypertension](#)
- ▶ [Endothelial Dysfunction and Vascular Remodeling in Hypertension](#)
- ▶ [Management of Hypertensive Emergencies](#)
- ▶ [Methodology of Casual Blood Pressure Measurement](#)
- ▶ [Neurohumoral and Autonomic Regulation of Blood Pressure](#)
- ▶ [Pharmacologic Treatment of Pediatric Hypertension](#)
- ▶ [The Role of ABPM in Evaluation of Hypertensive Target-Organ Damage](#)

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## Abstract

Few data are available on either the epidemiology or management of hypertension in older adolescents and young adults, leading to consensus recommendations for the management of hypertension in young adults aged 18 and all adults 60 years and below. The lack of guidance on cardiovascular risk modification is further compounded by limited health insurance coverage and acquisition of poor lifestyle choices, all of which contribute to the development of atherosclerotic disease and other target organ insults. This chapter will review the limited data on hypertension and its management in individuals aged 18–25, as well as the incontrovertible evidence that hypertension and atherosclerosis are progressive conditions that have their origins in the young. Societal interventions such as education regarding appropriate lifestyle choices and expansion of health insurance coverage may be the most appropriate strategies to prevent development of cardiovascular disease later in life.

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## Keywords

Blood pressure • Hypertension • Young adulthood • Atherosclerosis

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## Introduction

Hypertension affects one in three adults in the USA. There is usually a slow progression of elevated blood pressure (BP) beyond what is optimal (<115/75; Lewington 2002) to hypertensive (>140/90) over time. The ultimate determination of a patient as hypertensive by the observant health-care professional (or patient) may take time to recognize as the sustained measurements that meet the criteria for hypertension are documented. The concept of BP as progression through optimal levels to prehypertensive to

hypertensive may be instructive and illustrative of the cardiovascular (CV) risk factors and their influence on the pediatric population through young adulthood ages 18–25 years old and thereafter. What happens to the adult exposed to years of hypertension or prehypertension are likely a cumulative effect of the impact on the vasculature and the target organ exposure to this potentially unrestrained hemodynamic insult throughout one's life and not just as someone has an increased risk for CV disease at ages greater than 50 or 60. When we do not engage in studying the goals of BP control in adolescents, we then are limited in our ability to modify what this disease may do to those who age beyond this.

However, we do know that prehypertension unabated leads to hypertension. The overall prevalence of prehypertension (systolic BP of 120 to 139 mmHg and a diastolic BP of 80–89 mmHg) in adults was 28% of the US population based on data from the National Health and Nutrition Examination Survey (NHANES) 2005–2006 (Ventura and Lavie 2011; Ostchega et al. 2008). There is a heightened risk of progression to hypertension depending on lower or higher degrees of prehypertension (Winegarden 2005). Among people with BP 130 to 139 mmHg systolic and/or 85 to 89 mmHg diastolic (stage 2 prehypertension), the risk of developing hypertension is threefold that of normotensives with BP <120/<80 mmHg (Selassie et al. 2011). Indeed, the continuous relationship with risk throughout the normal range of usual BP, above 115/75 in those age > 40, is strongly and directly related to vascular and overall mortality (Lewington 2002). Data from the Framingham Heart Study suggest that individuals who are normotensives at 55 years of age have a 90% lifetime risk for developing hypertension (Chobanian et al. 2003; Vasan et al. 2002). This illustrates that the aging process leads to the inevitability of hypertension in the Western world. Because hypertension is a major risk factor for CV and cerebrovascular disease, two of the leading causes of death in adult Americans, responsible for 25% and 10% of all annual deaths respectfully, as well as an enormous cost to health care; improvements in education, accurate and accessible measurements, early

detection, risk modification and pharmaceutical treatment, as well as health insurance coverage is essential to reducing the burdens of the most common health-care malady in the USA.

This chapter is devoted to the young adult ages 18–25. The study of BP in pediatric patients and their target organ injury has been described in preceding chapters. The singular question is at what age hypertension should be treated to prevent ensuing target organ injury and to what degree in this population? Is there futility or benefit of controlling hypertension to reduce the untoward injury of repeated stress to the vessels and organs at the end of the vasculature? These adults aged 18–25 are not represented significantly in many of the landmark BP trials (Table 1) which will be discussed later. Given the paucity of data on outcomes of hypertension in this age group, this chapter will not present specific information on treatment goals. However, it will attempt to address the compelling question of what point in time, or age, does the vasculature sustain injury and therefore necessitate treatment. Whether the elevated BP is permanent or transient in nature because of modification of lifestyle or pharmaceutical management, the evidence appears to be mounting that treatment is of benefit.

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## Cardiovascular Death Trends and Age Groups

Cardiovascular disease in 2010 accounted for approximately 30% of all deaths in the USA, about 800,000 (Murphy et al. 2013). Deaths from CV and cerebrovascular disease can be avoided through improving lifestyle behaviors, treating modifiable risk factors, and addressing social determinants of health. From 2001 to 2010, the mortality data from the National Vital Statistics System were analyzed amid the improvements in risk factors and changes in cardiac treatments (CDC 2013; Ford and Capewell 2011). From 2001–2010, the avoidable death rate from heart disease, stroke, and hypertensive disease decreased 29% overall. The average annual percentage change (AAPC) shows that rates decreased sharply for 65–74-year-olds

**Table 1** Landmark hypertension trials

Study	Year	Age criteria	Reference
Syst-Euro	1997	≥60	(Staessen et al. 1997)
HYVET	2008	≥80	(Beckett et al. 2008)
SHEP	1991	≥60	(SHEP 1991)
ACCORD	2010	≥40	(Cushman et al. 2010)
SPS3	2013	≥30	(Benavente et al. 2013)
JATOS	2008	≥65	(JATOS 2008)
VALISH	2010	≥70	(Ogihara et al. 2010)
Cardio-Sis	2009	≥55	(Verdecchia et al. 2009)
HDFP	1979	30–39	(Hypertension 1979)
MRC	1985	35–64	(MRC 1985)
VA-COOPERATIVE	1967	30–73	(VA Cooperative 1967)
HOT	1998	50–80	(Hanson et al. 1998)
REIN	1999	18–70	(Ruggenti et al. 1999)
AASK	2002	18–70	(Wright et al. 2002)
MDRD	1999	18–70	(Klahr et al. 1994)
UKPDS	1998	25–65	(UK Diabetes 1998)
ADVANCE	2007	≥55	(Patel et al. 2007)
IPPSH	1985	40–64	(IPPSH 1985)
LIFE	2002	55–80	(Dahlof et al. 2002)
ALLHAT	2003	≥55	(ALLHAT 2003)
ONTARGET	2008	≥55	(Yusuf et al. 2008)
IDNT	2001	30–70	(Lewis et al. 2001)
RENAAL	2001	31–70	(Brenner et al. 2001)
The effect of ACE-I on DN	1993	18–49	(Lewis et al. 2001))
SRPINT	2015	≥50	(SPRINT 2015)
DASH	1997	≥22	(Appel et al. 1997)
INTERSALT	1988	20–29	(Intersalt 1998)

(AAPC = −5.1%), declined more gradually for 55–64-year-olds (AAPC = −3.3%), even more gradually for 35–54-year-olds (AAPC = −0.8%), and did not change at all in 0–34-year-olds. The death rate in 2010 for 0–34-year-olds was 1.9 per 100,000 population versus 401.5 per 100,000 in those aged 65–74 – compared to 640 per 100,000 in 2001 for the same age group (CDC 2013). This illustrates the benefits of improvements in risk factors and changes in CV treatments (Towfighi et al. 2011). However, as noted, there was no change in mortality for those between the ages of 0–34 years. Reasons for slower declines in death rates among younger populations may be attributable to greater benefits in modifying risks for older people, or in better health insurance coverage for those older than 65, or unavoidable losses in youth that could never be modified by any population-wide intervention.

## Health Insurance and Blood Pressure Control

In adults aged 18–64 years, the percentage of those without health insurance increased from 17% in 2001 to 22% in 2010 but remained at <2% among adults aged >65 years because of Medicare coverage in this population (CDC 2013; US Census Bureau 2012). The increase in percentage of those without insurance among the younger age groups might have limited their access to preventive screenings and early treatment of high BP and other health-care interventions to reduce CV risk factors. Compared with persons aged ≥60 years, during 2009–2010, adults aged 18–39 years with high BP experienced lower rates of treatment (43.5% versus 83.6%) and control (28.6% versus 47.0%)

**Table 2** Blood pressure treatment and control by age group, 2009–2010

Age group	18–39 years	>60 years
Hypertension treated	43.5%	83.6%
Hypertension controlled	28.6%	47%

**Table 3** Hypertension prevalence and control by age group and gender, 2011–2014

Age/gender	20–24/ male	20–24/ female	65–74/ male	65–74/ female
Hypertension prevalence	6.9%	4.3%	63.4%	64.3%
Hypertension control	25.9%	44.5%	61.8%	55.5%

(Table 2) and saw no improvements in those rates from 2001 to 2010 (Centers for Disease Control and Prevention 2013; US Census Bureau 2012). From 1997–2006, stroke hospitalization rates decreased among those 55–64 years old; stayed the same for those aged 45–54, and actually increased in those aged 35–44 years old (Towfighi et al. 2011). Those aged 18–25 were not analyzed. CDC data for young adults with hypertension ages 20–24 from 2011–2014 (Table 3) was 6.9% of males and 4.3% of females, and uncontrolled high BP was seen in 74.1% of the males and 55.5% of the females. These numbers for the same years 2011–2014 in those 65–74 years old demonstrated hypertension in 63.4% of the male and 64.3% of the female population with uncontrolled BP in 38.2% of males and 44.5% of females (National Center for Health Statistics 2016).

The point is clear that BP increases as we age, and management improves similarly, and uncontrolled hypertension in young adults is far greater than in the elderly. In 2014 for those under 18 years old, 6.5% had no health insurance coverage (Table 4) compared to 18.1% uninsured in those aged 18–24 years old, 22.7% for those aged 25–34, 17.7% in those aged 35–44, and 11.8% for those aged 45–65 (National Center for Health Statistics 2016). The control of BP parallels insurance coverage. The Affordable Care Act (ACA) and its expanded coverage of young adults who can stay on their parents' plans until they turn 26 likely influences not only coverage but also

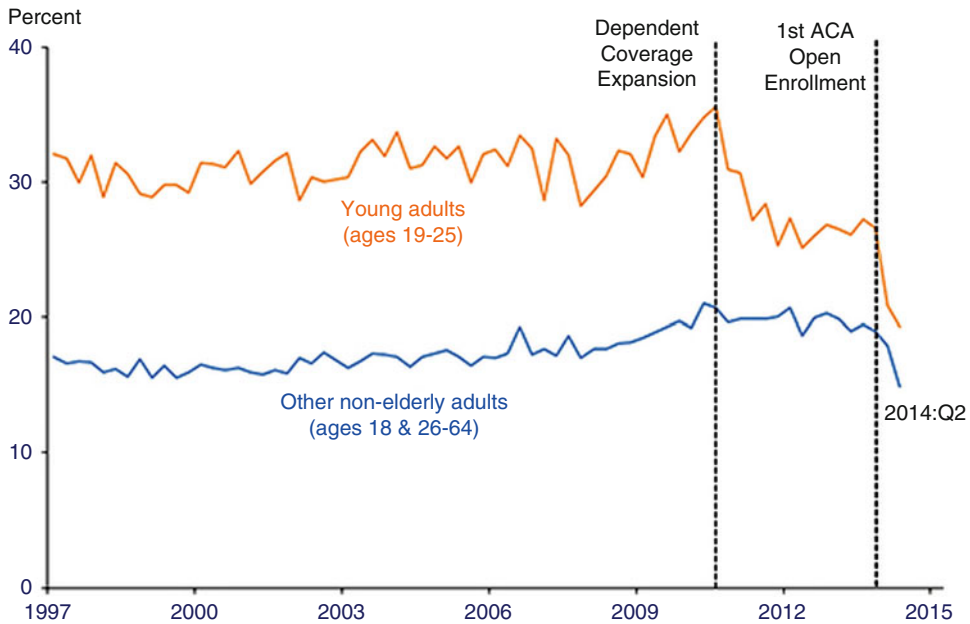
potentially treatment and control. An estimated 20 million uninsured people have gained health coverage, and a large number of these (an estimated around 2.3 million) are young adults ages 19–25 who gained health insurance between the enactment of the ACA in 2010 and the initial open enrollment period in October 2013 (Fig. 1) (Furman and Fielder 2015; Ueberoi et al. 2016). Whether this will impact CV complications as these young people age will only be understood over time.

### Cardiovascular Risk Assessment

Reliable approaches to scoring 10-year and lifetime CV disease (CVD) risk for those >50 years old according to the presence or absence of specific risk factors have been developed. These risk factors were smoking history, body mass index (BMI), BP, cholesterol levels, and presence or absence of diabetes. Framingham Heart Study participants had risk factor assessments and were free of CVD (myocardial infarction, coronary insufficiency, angina, stroke, claudication) at 50 years of age. Those with optimal risks at age 50 had lifetime risks of atherosclerotic CVD to 95 years of age of 5.2% for men and 8.2% for women. This compared to participants with more adverse levels of single risk factors, who had lifetime risks of CVD events that were higher: 52.7% for men and 39.2% for women in the entire cohort studied (3564 men and 4362 women). The risk reduction in CVD events was 90% for men and 79% for women if participants did not have any risk factors at age 50 (Lloyd-Jones et al. 2006). Increasing BP and total cholesterol were associated with increased lifetime risk for CVD and shorter median survival, and the presence of diabetes at 50 years of age conferred the highest lifetime risk for CVD of any single risk factor. Median survival was substantially lower among diabetics compared with nondiabetics (Lloyd-Jones et al. 2006). Similarly, overweight status and obesity were associated with modest increases in lifetime risk and reductions in survival compared with normal weight status.

**Table 4** Uninsured populations by age, 2014

Age	<18	18–24	25–34	35–44	45–65	>65
Uninsured	6.5%	18.1%	22.7%	17.7%	11.8%	<2%



**Fig. 1** Adult uninsured rates, 1997–2014 (Source: Furman and Fielder 2015)

With respect to the continuum of disease, a 50-year-old patient does not flip a switch that has a sudden impact on one’s CVD risk and adverse outcomes. The influence of the perturbed milieu of metabolic and mechanical abnormalities is a steady continuum during one’s life that leads to detrimental effects on target organs, including the heart, brain, and kidneys. Clearly, behavioral habits and preventive efforts need to begin decades before the age of 50, since even the presence of a single major risk factor at that age is associated with substantially increased lifetime risk for CVD and markedly shorter survival (Lloyd-Jones et al. 2006). Patients who are 50 years of age or younger may have a very high lifetime CVD risk, which may be amenable to risk factor reduction but may be considered to be at low risk because they have a low 10-year CV risk (due to the weighting of age

in 10-year risk equations) (Berger et al. 2010). Since the estimates for 10-year risk prevalence nationally for most men <50 years and most women <70 is <10%, it becomes difficult to capture the risk in those <30 years. This is illustrated in studies using the Framingham Risk Score (FRS) that classified all men <30 years as “low risk” by Adult Treatment Panel III definitions, despite a substantial risk factor burden (Berry et al. 2007; Ford et al. 2004). Therefore, the use of long-term (>30-year) risk assessment tools is necessary. Similarly necessary are recommendations for the institution of treatment prior to actual occurrence of clinical events. These shorter-term strategies have no effect on lowering short-term risk in younger patients and suboptimal effects on longer-term risk, since treatment introduced at some older age does not eliminate



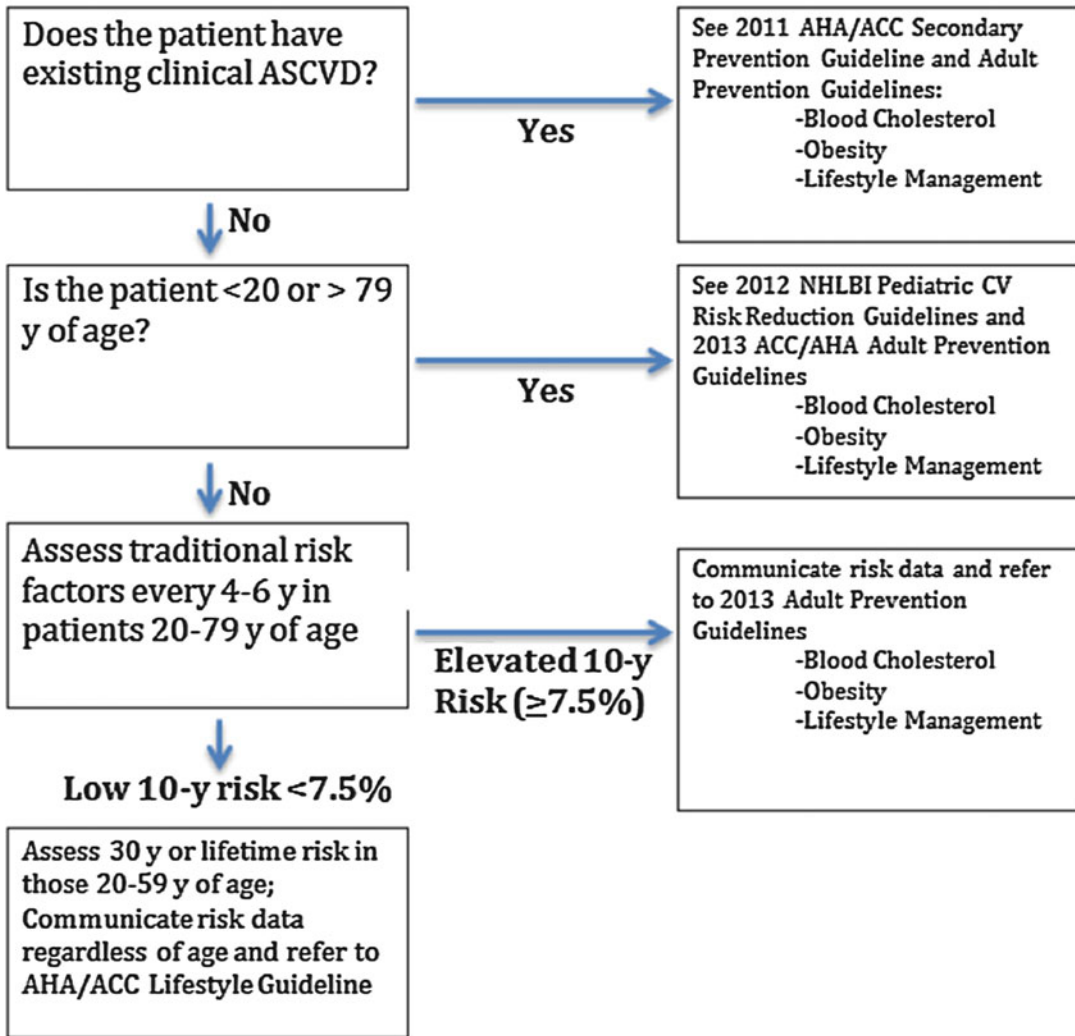
decades of exposure to high-risk factors. On the other hand, overweighting lifetime risk without studied outcomes beginning at an early age may potentially commit large numbers of individuals to lifelong drug therapy with unknown consequences (Cavanaugh-Hussey et al. 2008).

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline on the assessment of CV risk calculates the 10-year risk of heart disease or stroke and predicts risk in those with ages between 20 and 70. Extensive epidemiological, pathological, and basic science data indicate that the development of atherosclerosis, the precursor to atherosclerotic CV disease (ASCVD), occurs over decades and is related to long-term and cumulative exposure to causal, modifiable risk factors. In assessing for evidence of risk factors in young adults, individuals with extreme values for BP, particularly from secondary hypertension or familial hyperlipidemia, may be identified, and as a population data on risk prevalence and consequences may be studied for future benefit of lifestyle modification and or pharmaceutical treatment (Goff et al. 2014). The 2013 ACC/AHA guideline 6.2.2 recommendation 2 for long-term assessment of 30-year or lifetime ASCVD risk based on traditional risk factors may be considered in adults 20–59 years of age who are free from ASCVD and who are not at high short-term risk. The evidence here is weak, with very limited populations evaluated and only consensus opinion of experts, case studies, or standard of care. With respect to benefit of treatment versus risk for treatment, the usefulness/efficacy of lipid management is less well established (Goff et al. 2014). Also, evidence was not found regarding the utility of lifetime risk assessment for guiding pharmacologic therapy decisions, and the work group judged that long-term and lifetime risk information may be used more appropriately at that time to motivate therapeutic lifestyle change in younger individuals, and the choice of age 20 as the starting point for long-term risk assessment was used as a starting point for long-term risk assessment. Figure 2 illustrates their approach to these populations (Goff et al. 2014).

## Blood Pressure Goal

The US Preventive Screening Task Force (USPSTF) recommends annual screening of BP for adults aged 40 years or older for those who are at increased risk for high BP, those with prehypertension 130–139/85–89 mm Hg, overweight or obese, and African Americans. Adults aged 18–39 years with normal BP (<130/85) who do not have other risk factors should be rescreened every 3 to 5 years (Siu AL; US Preventive Services Task Force 2015). (Note: their use of the term normal BP is not the same as optimal [<115/75 mmHg] referenced elsewhere in this chapter.) The USPSTF recommends screening for high BP in adults aged 18 years or older and gives it an A recommendation. (There is high certainty that the net benefit is substantial.) This means the available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. The conclusion is therefore unlikely to be strongly affected by the results of future studies.) Furthermore, obtaining measurements outside of the clinical setting for diagnostic confirmation before starting treatment is also recommended.

Once the diagnosis of hypertension has been made in a young adult aged 18–25, management, particularly in someone who has coronary and other atherosclerotic disease, would be similar to recommendations for other adults based on the 2011 AHA/ACC guidelines, because no distinction for age is made. In light of the SPRINT study, evidence for those aged >50 with SBP 130–180 mmHg untreated or treated with antihypertensive medications and at increased risks of CV events was that an SBP of 120 mm Hg resulted in lower rates of fatal and nonfatal major CV events and death from any cause (The SPRINT Research Group 2015). However, the age group from 18–25 was not studied. Does this mean there should be another goal if those 18–25 years of age have coronary and other atherosclerotic disease? What is the goal for these young adults who could be possibly at increased risk for CV events? The recommendations from members of the Joint



**Fig. 2** Implementation of ACC/AHA risk assessment work group recommendations. *ACC*: American College of Cardiology; *AHA*: American Heart Association;

*ASCVD*: atherosclerotic cardiovascular disease (Source: Goff et al. 2014)

National Committee panel stated that there is insufficient evidence from good or fair quality randomized controlled trials (RCTs) to support in hypertensive persons younger than 60 years a specific systolic goal, or in those younger than 30 years a specific diastolic goal, so based upon expert opinion, the panel recommended a goal BP of less than 140/90 mmHg for these groups (James et al. 2014). More specifically, for ages 18–29 years, the systolic BP goal is <140 mmHg and diastolic BP goal is <90 mmHg, and this is completely based on expert

opinion due to the lack of clinical trial evidence in this age group. With the release of SPRINT, future consensus bodies may change recommendations for those age  $\geq 50$  at increased CV risk, but for those ages 18–25, the goal systolic BP is the same as for those 25–49. Given the difficulty of informing and controlling this population, this is likely a good starting point for control. Nonetheless, both systolic and diastolic BP goals should be studied and extended to those less than the age of 50. There were several studies in Table 1 that included participants that were ages 18–25. To our

knowledge the data were not analyzed separately for this age group, and there were too few patients within this age range, particularly in the MDRD and AASK trials, to yield useful information in managing them.

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## Atherosclerosis in Young Adults

The ability to assess atherosclerotic disease in the young adult population is irrecoverably linked to series of autopsy studies, including some conducted on combat fatalities, and others from population-based studies. The coronary arteries of 200 soldiers with the average age of 22 years who were killed in the Korean War demonstrated some evidence of coronary arteriosclerotic disease in 77.3% (Enos et al. 1953). Two decades later during the Vietnam War, postmortem coronary angiography and dissection of the hearts from 105 US soldiers (mean age of 22 years, range 18–37 years) demonstrated that 45% had some evidence of atherosclerosis, although none had angiographic evidence of severe coronary narrowing (Strong and McGill 1962).

A community-wide evaluation of atherosclerosis was conducted in New Orleans in 1962 as part of the Bogalusa Heart Study, reviewing 548 necropsies. Data on CV risk factors were collected cross-sectionally beginning in 1973 on 14,000 people from birth until the age of 38, with periodic repeat assessments. Autopsies were performed after the death of a young person (most deaths were due to accidents or homicide) to evaluate for pathological atherosclerotic findings in coronary arteries and aorta (Berenson et al. 1998). Coronary arteriosclerosis was found in those as young as 10–19 years old, with increasing prevalence paralleling age; these lesions were noted at least 20 years of age earlier than in the combat victim autopsy study mentioned previously (Strong and McGill 1962). Crucially, the investigators were able to link pathologic findings to antemortem CV risk factors. Specific antemortem risk factors such as elevations in BMI, systolic BP, serum triglycerides, LDL cholesterol concentration, and cigarette smoking were significantly related to the extent of atherosclerotic lesions in young

people and are in agreement with the findings in other studies. With respect to these studies on populations in the twentieth century, presumably with the incidence of obesity, diabetes, and hypertension more prevalent in the twenty-first century, we would expect more pathologic lesions. This illustrates the occurrence of vascular disease that occurs in young healthy adults and the need to consider risk factor reduction management in this population despite the lack of studies to reduce CV disease outcomes. The chapter in this text on Epidemiology of Cardiovascular Disease in Children reviews this concept as it pertains to the pediatric population as well as those risk factors in childhood that predict atherosclerosis in adulthood.

The landmark Pathobiological Determinants of Atherosclerosis in Youth Study (PDAY) (McGill et al. 2008) is important to mention as well. This study examined autopsies looking at coronary arteries and aortas, estimating the percentage of intimal surface involved by fatty streaks and atherosclerotic lesions in persons 15 through 34 years of age who died of external causes (accidents, homicides, and suicides). Labs for total and lipoprotein cholesterol, glycohemoglobin, and thiocyanate levels to indicate smoking were drawn to assess exposure to these risks factors. Wall thickness of small renal arteries was measured to estimate mean arterial BP (increased renal artery thickness indicated hypertension), and BMIs were determined postmortem for obesity assessment. There was a relationship among 15–34 years of age between CV risk factors and quantifiable vascular injury. PDAY results have confirmed previous observations that atherosclerosis begins in childhood and progresses into young adulthood and beyond. By the third decade, many young adults already have significant coronary atherosclerosis, which includes not only calcified plaques seen by radiography but also carotid intima-media thickness seen on noninvasive methods. Intervention in the fourth decade and after may be too late for optimal CVD prevention (McGill et al. 2008). The theoretical and plausible likelihood of vascular injury in youth persisting to adulthood unless modified by risk reduction begs the question, when will researchers study the

effects of intervention during youth to reduce the composite CV injury studied in adults of age greater than 50 as in such studies as the SPRINT BP trial?

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### **Fitness in Young Adulthood and Cardiovascular Disease**

Health fitness in the form of cardiopulmonary fitness is an established lifestyle attribute that modifies CV disease. A population-based longitudinal cohort study of 18–30-year-olds was studied in the Coronary Artery Risk Development in Young Adults (CARDIA) study (Carnethon et al. 2003). Participants who completed the treadmill examination protocol at baseline were followed up over 15 years. The main outcome measure was incident type 2 diabetes, hypertension, and the metabolic syndrome. During the 15-year study, the rates of incident diabetes, hypertension, and metabolic syndrome were assessed. Those participants with fitness <20th percentile were 3–6-fold more likely to develop diabetes, hypertension, and the metabolic syndrome than participants with fitness > 60th percentile. Improved fitness over 7 years was associated with a reduced risk of developing diabetes and the metabolic syndrome (Carnethon et al. 2003). Poor fitness in young adults followed longitudinally is associated with the development of CVD risk factors with low fitness increasing hypertension by 21% and diabetes 28%. Fitness in young adults has CV benefits, and the lack thereof has consequences that extend for decades.

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### **Young Adult Lifestyle Attributes that Lend Themselves to Hypertension and Cardiovascular Disease**

Data from the CDC 2011–2014 sheds light on several risk factors for CV disease and hypertension that could be modified by 18–25-year-olds to influence future outcomes. Males and females from 20 to 34 years old have a prevalence of obesity from 28.5% and 33.4%, respectively (National Center for Health Statistics 2016;

Table 58). Among 12–19-year-olds obesity in both sexes was 20.5% of the population (National Center for Health Statistics 2016; Table 59). One can surmise that there is a steady rise in young adulthood and onward. In the ensuing decade from ages 35–44, they have a prevalence of obesity of 39%, and this changes little for males but goes up to 44.4% in females 55–65 years of age.

With respect to participation in both leisure-time aerobic and muscle-strengthening activities that meet the federal 2008 Physical Activity Guidelines for Americans among adults aged 18 and over, a recent analysis revealed for 18–24-year-olds, 31% met both these guidelines in 2014, but this figure declined to 25% for ages 25–44 years and continued to decrease for each decade thereafter (National Center for Health Statistics 2016; Table 57). Obesity and a sedentary lifestyle go hand-in-hand and tend to worsen as we age.

To reinforce the health-care coverage issue, which likely plays a role in awareness of health and management, in 2013–2014 for ages 19–25, there were 28.5% of young adults who did not have a usual source of health care (distinct from no health insurance coverage), and compared to those ages 6–17 years old who did not have usual sources of health care, they were about 4.4% (National Center for Health Statistics 2016; Tables 61 and 62). This is compared to those 25–44 years old where 22.8% did not have a usual source of health care, and from 45–54 years, it is 12.8%, and from 55–64, it is 8.6% (National Center for Health Statistics 2016; Table 61).

Smoking as a risk factor for CV events is a public health issue, and of note in 2013–2014, CDC data indicates that cigarette smoking in 18–24-year-olds was 18.5% for males and 14.8% for females and increased in 25–34-year-olds to 23.7% and 17.5% in males and females, respectively. This relationship between lower health insurance coverage (Table 4) for 25–34-year-olds may be telling. However, those over 25 years old had a usual source of health care greater than the 19–25-year-olds. Perhaps health-care personnel needs to be more vigilant in noting and modifying CV risk factors, or those in that age group need to be better informed of the risks of

smoking. Smoking cessation in later decades decreases for each decade thereafter.

It appears when looking at obesity, physical activity, smoking, and hypertension, the tipping point to the development of good or bad habits or increased or decreased risk factors for CV disease occurs in adults in the 18–25-year age group. After this, physical activity typically diminishes, obesity skyrockets, smoking prevalence increases, and the prevalence of hypertension in the population increases, with control rates <50% of the population until we are 45–54 years old. To add further insult, health insurance and usual sources of health care is not as utilized or available for the young adult at this time in their life. Clearly the young adult does not have financial coverage or incentives to have CV risk assessed, screened, or managed. The psychology of this is likely related to the invincibility of youth as well as the distractions of moving into lifelong employment, careers, and their own relationships and families outside their childhood formative years. It would seem that for those 18–25 years old, a transition into adulthood with significant medical guidance would be warranted to avoid irreparable harm from a stroke, heart attack, or incessant atherosclerosis destined for a significant part of our population.

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## Summary

Recognizing lifetime risk at an early age should provoke policy makers and an informed electorate to better promote public interest in prevention, screening, studying and treatment of CVD especially in younger adults who have more years at risk to protect from CV harm when risk modification has more potential benefit. This information could potentially guide the allocation of resources to improve public health and preventive services for the leading cause of death in the USA. Discrepancies in health insurance coverage, uncontrolled high BP, lack of studies directed at this population, and lifestyle factors expose future 50-year-olds to CV risk and injury over time. The 2016 scientific statement from the

American Heart Association, “Cardiovascular Health Promotion in Children: Challenges and Opportunities for 2020 and Beyond,” delivers this summation. The principles in their summary reflect the AHA’s new dynamic and proactive goal to promote CV health throughout the life course. “The primary focus is on adult CV health and disease prevention, but critical to achievement of this goal is maintenance of ideal CV health from birth through childhood to young adulthood and beyond” (Steinberger et al. 2016).

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## Cross-References

- ▶ [Epidemiology of Cardiovascular Disease in Children](#)
- ▶ [Value of Routine Screening for Hypertension in Childhood](#)

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### Abstract

Hypertension is a major global chronic non-communicable disease (NCD). Due to epidemiologic shifts, the absolute numbers of patients affected by hypertension in low- and middle-income countries are likely to grow, as increased globalization and economic improvement lead to urbanization and longer life expectancy. Increasing longevity provides longer periods of exposure to the risk factors of cardiovascular disease (CVD), resulting in a greater probability of clinically manifesting CVD events. Compounding this high burden of hypertension is a lack of awareness and insufficient treatment in those with hypertension. Additionally, survivors of an economic transition period are more likely to present the phenotype of lower birth weight coupled with either stunting or a higher body mass index in childhood or adulthood, which appears to be associated with the highest risks of morbid cardiovascular, renal, and metabolic outcomes into adulthood. The combination of population-wide and individual interventions may save millions of lives and considerably reduce human suffering from NCDs.

### Keywords

Hypertension • Developing world • Non-communicable diseases • Global disease burden • Epidemiological transition • Fetal origins of adult disease • Malnutrition • Low birth weight

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## Introduction

In the past, the diseases that have occurred among people in developed and developing countries have largely been attributed to the socioeconomic status of each country (Omran 1971). In developed countries, most of the health problems have been those associated with increased wealth, sedentary lifestyle, and increased fat intake. In contrast, the diseases that have occurred among people in developing countries have been largely attributed to poverty, poor infrastructure, and limited access to care. These factors lead to famine, the spread of infectious disease, and reduced lifespans.

Economic development traditionally leads to change from times of high mortality and low population growth to periods of increased lifespan and receding pandemics. The final progression resulting from major social and economic changes is to degenerative and manmade diseases, such as cardiovascular disease (CVD) (Omran 1971). In modern times, however, the transition is happening at a faster pace due to urbanization, free trade and economic globalization, foreign investment, and promotional marketing (Yach 2004).

Life expectancy in developing countries has risen, due to a decline in infant and childhood deaths, to increased effectiveness of public health responses to perinatal, infectious, and nutritional deficiency disorders and to improved economic status such as per capita income and social indicators such as female literacy in some areas. Increasing longevity provides longer periods of exposure to the risk factors for CVD, resulting in a greater probability of clinically manifesting CVD events (Reddy 1993; Mittal and Singh 2010) and leading to a projected rise in both proportional and absolute CVD mortality rates in the developing countries (Omran 1971).

A total of 56 million deaths occurred worldwide during 2012. Of these, 38 million were due to noncommunicable diseases (NCDs), principally cardiovascular diseases, cancer, and chronic respiratory diseases. Nearly three quarters of these NCD deaths (28 million) occurred in low- and middle-income countries. NCD deaths have

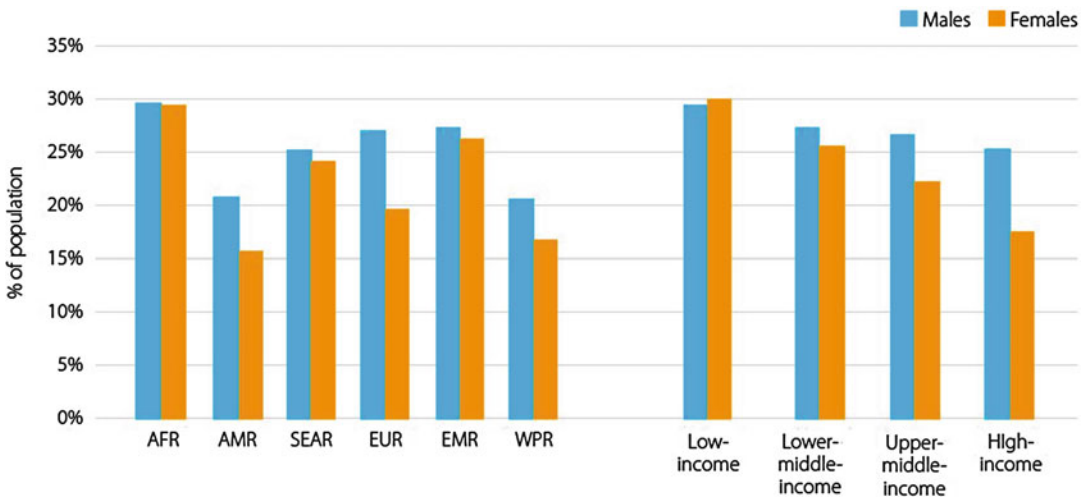
increased the most in the World Health Organization (WHO) Southeast Asia Region, from 6.7 million in 2000 to 8.5 million in 2012, and in the Western Pacific Region, from 8.6 to 10.9 million (WHO 2014).

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## Hypertension and CVD in the Developing World

Hypertension is a major global chronic NCD and a leading risk factor for CVD. The global prevalence of raised blood pressure (defined as systolic and/or diastolic blood pressure  $\geq 140/90$  mmHg) in adults aged 18 years and over was around 22% in 2014 (WHO 2014). Across the WHO regions, the prevalence of raised blood pressure was highest in Africa, at 30% for all adults combined. The lowest prevalence of raised blood pressure was in the region of the Americas, at 18% (Fig. 1).

In 2012, cardiovascular diseases were responsible for 17.5 million deaths, or 46% of all NCD deaths, and diabetes caused another 1.5 million deaths (WHO 2012). Figure 2 shows the age-standardized, per 100,000, CVD mortality for both sexes in 2012 (Causes of Death WHO 2012). Of these deaths, an estimated 7.4 million were due to coronary heart disease, and 6.7 million were due to stroke (WHO 2012). Around one third of these CVD deaths occur prematurely in adults aged 30–70. Premature mortality rates due to NCDs declined globally by 15% between 2000 and 2012, mainly because of a decrease in CVD mortality, driven by population-level blood pressure improvements, declines in tobacco use, and advances in medical treatment. Declines have been greater in high-income countries than in the low- and middle-income countries (WHO 2015). Although population-level blood pressure improvements are a likely major contributor to declining CVD mortality rates in many countries, not all regions are making progress at the same rate, and several countries have recorded increases in population-level blood pressure. Reasons for this include inadequate reduction (or even increase) in tobacco use, high levels of sodium



**Fig. 1** Age-standardized prevalence of raised blood pressure in adults aged 18 years and over across WHO regions and World Bank income groups. *AFR* African region, *AMR* region of the Americas, *SEAR* Southeast Asia region, *EUR*

European region, *EMR* Eastern Mediterranean region, *WPR* Western Pacific region (Source: Global status report on NCD, WHO, Geneva 2014)

consumption, and lack of access to appropriate health care, including effective medication such as antihypertensive medicines and statins (WHO 2015; Ezzati et al. 2015).

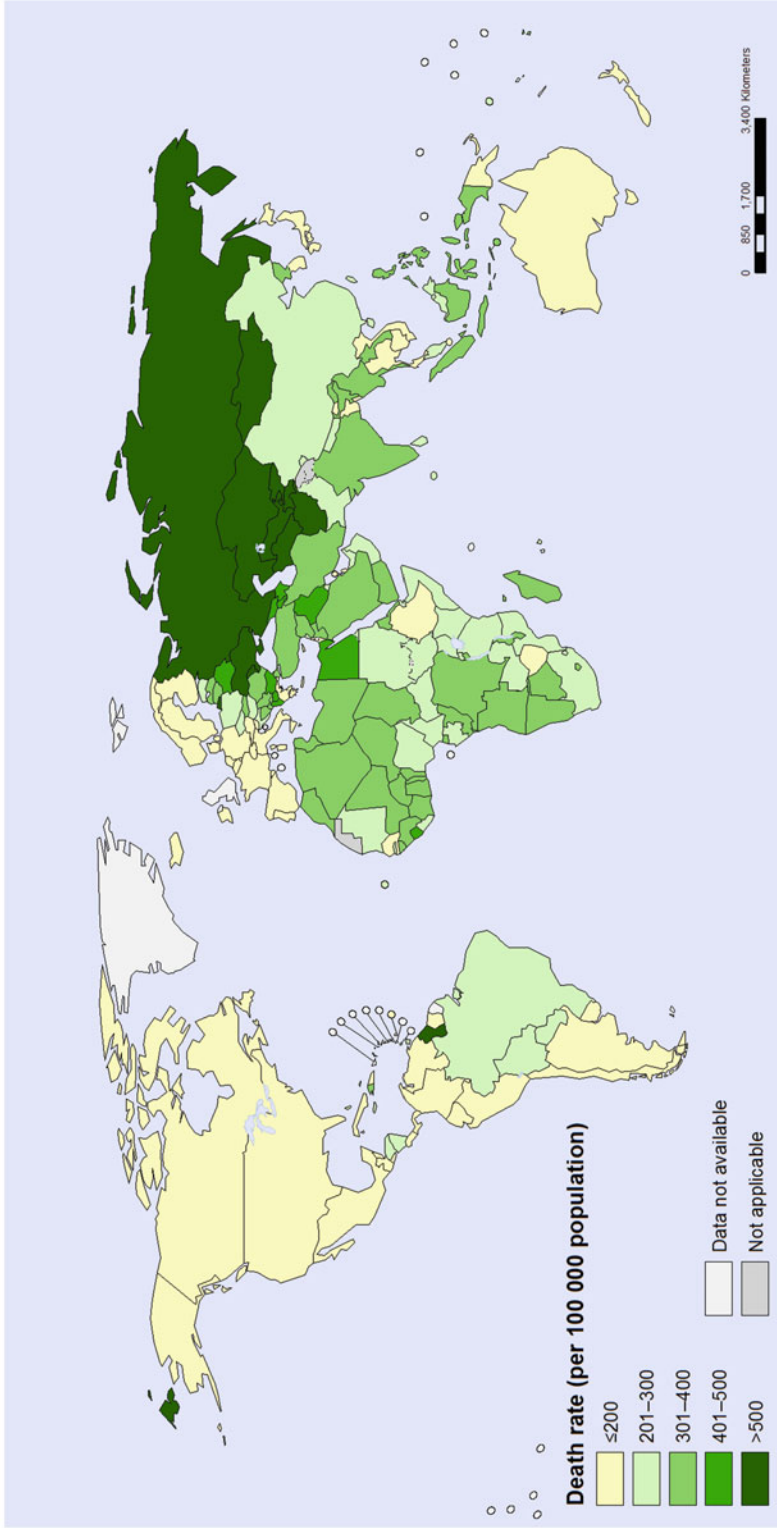
Eight risk factors (alcohol use, tobacco use, high blood pressure, high body mass index, high cholesterol, high blood glucose, low fruit and vegetable intake, and physical inactivity) account for 61% of cardiovascular deaths. Combined, these same risk factors account for over three quarters of ischemic heart disease, the leading cause of death worldwide. Although these major risk factors are usually associated with high-income countries, over 84% of the total global burden of disease they cause occurs in low- and middle-income countries. Reducing exposure to these eight risk factors would increase global life expectancy by almost 5 years (WHO 2009). Several studies from different continents have documented the higher prevalence of hypertension in urban versus rural populations (Kearney et al. 2005; Gupta and Sharma 1994; Gupta et al. 1995; Wang et al. 2004; Mbanaya et al. 1998; Addo et al. 2007). Urbanization often is associated with increased income and adoption of an unhealthy lifestyle, including the adoption of unhealthy food habits characterized by a diet rich in salt, saturated

fats, and poor-quality carbohydrates, typical of fast foods (Yach 2004; WHO 2002).

An aggravating factor in the CVD epidemic in developing countries might be that the normal range of BMI cutoff values derived from Western population may be misleading when applied to other ethnic groups (Razak et al. 2007). Several reports suggest that in the Chinese, South Asian, and Aboriginal populations, higher prevalence rates of dyslipidemia, metabolic syndrome, type 2 diabetes mellitus, and CVD are observed at a much lower BMI than in Europeans (Razak et al. 2007; Unwin et al. 1997).

Genetic differences may play a role, especially in relation to polymorphisms of the renin-angiotensin-aldosterone system (RAAS) genes, such as the association of the angiotensin gene 20A – C polymorphism, which confers a greater than expected increase in ambulatory systolic BP to any given BMI in African-descent hypertensive patients (Tiago et al. 2002). Other possible factors are a lack of stimulation of plasma renin activity by natriuresis with furosemide, suggesting a hyporesponsive RAAS in hypertensive urban Zulus (Touyz et al. 1987), and the high prevalence of salt-sensitive hypertension in hypertensives of African descent, pointing to an

### Cardiovascular diseases mortality: Age-standardized death rate per 100 000 population, both sexes, 2012



The boundaries and names shown on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

**Fig. 2** CVD mortality rates (age standardized per 100,000), both sexes, 2012 (Source: Causes of death 2012, WHO, Geneva)

abnormal renal hemodynamic adaptation during high salt intake (Campese et al. 1991).

Global efforts to address the challenge of NCDs have gained momentum since the 2011 United Nations Political Declaration on the prevention and control of NCDs, which led to the Millennium Development Goal (MDG) framework project. This project ended in 2015 and, in September 2015, was followed by the “Transforming our World: The 2030 Agenda for Sustainable Development,” which outlined a new framework to form the cornerstone of the sustainable development agenda for the period leading up to 2030 (WHO 2015).

The “Global Burden of Diseases, Injuries, and Risk Factors Study 2015,” which covered 79 risk factors or combinations of risks from 1990 to 2015 in 188 countries, is the most recent assessment of attributable deaths and disability-adjusted life years (DALYs) at the global, regional, and national level (GBD 2016 Risk Factors Collaborators). It provides an assessment of the strength of evidence supporting causality for 388 risk-outcome pairs. The DALY combines years of life lost due to premature death with years of healthy life lost due to illness and disability. Between 1990 and 2015, global exposure to unsafe sanitation, household air pollution, childhood underweight, childhood stunting, and smoking each decreased by more than 25%. On the other hand, the global exposure to high BMI increased by more than 25% over the same period. All risks jointly evaluated in 2015 accounted for 57.8% of global deaths and 41.2% of DALYs. In 2015, high systolic blood pressure, smoking, high fasting plasma glucose, high BMI, childhood undernutrition, high total cholesterol, alcohol use, and diets high in sodium were still among the ten largest contributors to global DALYs among level 3 risk factors. From 1990 to 2015, attributable DALYs declined for micronutrient deficiencies and childhood undernutrition, while rising exposure contributed to notable increases in attributable DALYs from high BMI and high fasting plasma glucose. Environmental risks and childhood undernutrition declined steadily with sociodemographic index (SDI); low physical activity, high BMI, and high fasting plasma

glucose increased with SDI. In 119 countries, metabolic risks, such as high BMI and fasting plasma glucose, contributed the most attributable DALYs in 2015. Regionally, smoking still ranked among the leading five risk factors for attributable DALYs in 109 countries; childhood underweight and unsafe sex remained primary drivers of early death and disability in much of sub-Saharan Africa (GBD 2016 Risk Factors Collaborators).

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### **The Fetal Origins Hypothesis and DOHAD: Developmental Origin of Health and Adult Disease**

The “early” or “fetal” origins of adult disease hypothesis, which states that perinatal factors, particularly nutrition, act in early life to program the risks for the early onset of cardiovascular and metabolic disease in adult life, were originally put forward and further developed by David Barker and colleagues in Southampton in the United Kingdom (Barker et al. 1989a, b, c, 1990, 1993a, b, 2002; Martyn et al. 1995; Barker 1995; Barker and Osmond 1986; Barker 2004;58:114–5). Before the fetal origins hypothesis was articulated, an association between early life events and later cardiovascular disease had been proposed on more than one occasion (Kermack et al. 1934; Forsdahl 1977; Wadsworth et al. 1985).

In 1992, Hales and Barker (Hales and Barker 1992) coined the term the “thrifty phenotype” hypothesis, derived from the prior “thrifty genotype” hypothesis (Neel 1962), proposed by Neel. Neel suggested that “thrifty” genes were selected during evolution, at a time when food resources were scarce, resulting in a “fast insulin trigger” and thus an enhanced capacity to store fat, placing the individual at risk of insulin resistance and type 2 diabetes when resources were no longer limited. The “thrifty phenotype” hypothesis, however, suggested that when the fetal environment is poor, there is an adaptive response, which optimizes the growth of key body organs to the detriment of others and leads to an altered postnatal metabolism, which is designed to enhance postnatal survival under conditions of intermittent

or poor nutrition. It was proposed that these adaptations only became detrimental when nutrition was more abundant in the postnatal environment than it had been in the prenatal environment (Hales and Barker 1992, 2001). This concept is consistent with the definition of “programming” as proposed by Lucas in 1991 (Lucas 1991) as either the induction, deletion, or impaired development of a permanent somatic structure or the “setting” of a physiological system by an early stimulus or insult operating at a “sensitive” period, resulting in long-term consequences for function. One of the crucial elements of this definition is the concept of a sensitive or “critical” period during which specific nutritional perturbations may operate to cause long-term changes in development and adverse outcomes in later life (Thoman and Levine 1970; Wiesel and Hubel 1965). Germ cell maturation, fertilization, blastocyst formation, differentiation, organogenesis, fetal growth and development, postnatal growth and development, puberty, and pregnancy are considered critical windows of developmental plasticity, and each stage can be affected by factors that may program adult disease (McMillen and Robinson 2005; West-Eberhard 2003; Bateson et al. 2004). As in other species, developmental plasticity attempts to “tune” gene expression to produce a phenotype best suited to the predicted later environment (Gluckman and Hanson 2004), and when the resulting phenotype is matched to its environment, the organism will remain healthy. When there is a mismatch between phenotype and environment, the individual’s ability to respond to environmental challenges may be inadequate, and the risk of disease increases. Thus, the degree of the mismatch determines the individual’s susceptibility to chronic disease (Gluckman et al. 2007).

The processes of phenotypic induction through developmental plasticity produce integrated changes in a range of organs via epigenetic processes. They establish a life-course strategy for meeting the demands of the predicted later environment (Gluckman et al. 2007) producing a range of effects in cardiovascular and

metabolic homeostasis, growth and body composition, cognitive and behavioral development, reproductive function, repair processes, and longevity, some of which are associated with increased risk of cardiovascular and metabolic disease, “precocious” puberty, osteoporosis, and some forms of cancer.

Understanding the underlying epigenetic processes thus holds the key to understanding the underlying pathophysiology and to developing approaches to early diagnosis, prevention, and treatment of these diseases. The term “epigenetic” was proposed by Waddington (Waddington 1957) to refer to developmental environment influences on the mature phenotype. It is now used to refer to structural changes to genes that do not alter the nucleotide sequence. Epigenetic marks encode information from both the inherited genotype and environmental exposures; they present a promising approach to explain multifactorial diseases and may potentially represent biomarkers for risk stratification and disease diagnosis (Ong et al. 2015). In brief, epigenetic mechanisms may include histone modification, RNA-dependent DNA methylation, paramutation, or RNA interference and transcriptional silencing (Heard and Martienssen 2014). Of particular relevance is methylation of specific CpG dinucleotides (cytosine and guanine adjacent to each other in the genome, linked by a phosphodiester bond) in gene promoters and alterations in DNA packaging arising from chemical modifications of the chromatin histone core around which DNA wraps. The modifications include acetylation, methylation, ubiquitination, and phosphorylation (Godfrey et al. 2007).

The degree of phenotype-environmental mismatch can by definition be increased by either poorer environmental conditions during development or richer conditions later, or both (Gluckman et al. 2007). In developing countries, vast numbers of poorly nourished infants born over the past several decades have been benefitting from a steady improvement in child survival, which will lead to a higher proportion of such infants surviving to adulthood life, with an increased risk for development of CVD.

## **Evidence of Epigenetic Mechanisms in Animals and Its Importance as a Cause of Adult Nephropathy and Arterial Hypertension**

Birth weight is a surrogate for the broad spectrum of specific adverse events that may impair fetal growth in humans; therefore, experimental models have been developed to probe postnatal outcomes after specific interventions that are relevant to human pregnancy, including nutrient deficits and placental insufficiency (Armitage et al. 2004). Attention continues to focus primarily on fetal growth. Impaired growth during this critical period of organ development may have an impact on future disease risk by permanently reducing the number of functional units, specifically nephrons (Bagby 2007).

Subsequently, investigators have developed animal models of perinatal programming that can be used to examine the impact of different interventions, ranging from the modification of the maternal or grandmaternal diet to the prenatal administration of glucocorticoids, ligation of the uterine artery, experimentally produced anemia, and alteration of postnatal growth (Mcmillen and Robinson 2005), on later health outcomes. These perturbations can result in the adverse development of organs or organ systems directly or in adaptive responses that may be beneficial in the short term but deleterious in the long run. Because such experiments in animals involve environmental changes, they do not address purely genetic influences, but epigenetic processes may play a key role in the mechanisms underlying these phenomena (Mcmillen and Robinson 2005).

The importance of the kidney in the long-term control of arterial pressure and in the pathogenesis of hypertension has been recognized since the seminal works of Guyton et al. showing the dominant role of the pressure natriuresis mechanism in the regulation of extracellular fluid volume (Guyton et al. 1972). In the late 1980s, Brenner et al. advanced the argument that deficiency in glomerular filtration surface area may be a major cause of primary hypertension (Brenner et al. 1988).

Several animal studies were devised to evaluate the effect of perinatal interventions on renal organogenesis and postnatal renal function. Table 1 depicts some of these studies and the main results in the offspring (Gilbert et al. 1991; Celsi et al. 1998; Lelièvre-Pégorier et al. 1998; Vehaskari et al. 2001; Woods et al. 2001; Pham et al. 2003).

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## **Evidence of Epigenetic Mechanisms in Humans and Its Importance as a Cause of Adult Nephropathy and Arterial Hypertension: A Potential Link to Hypertension and Metabolic Syndrome in Developing Countries**

Human studies have provided evidence suggesting nongenomic inheritance across generations. Patterns of smoking, diet, and exercise can affect risk across more than one generation (Brook et al. 1999). Body size at birth is correlated with placental size; however, at any birthweight, there is a wide range of placental weight (Alwasel et al. 2011). A baby's nutrition depends on the placenta's ability to transfer nutrients from the mother to baby and on the mother's nutritional state. Fetal growth in utero depends on their mothers' diets during pregnancy and on her metabolism (Jackson 2000), which is a product of her lifetime nutrition patterns, height, and weight (Tanner 1989).

During the 1944/1945 famine in the Netherlands, previously adequately nourished women were subjected to low caloric intake and associated environmental stress. Pregnant women exposed to famine in late pregnancy gave birth to smaller babies, and second-born infants of females exposed in the first trimester in utero did not have the expected increase in birth weight with increasing birth order (Lumey and Stein 1997). Famine exposure at different stages of gestation was variously associated with an increased risk of obesity, coronary heart disease, microalbuminuria, later insulin resistance, and dyslipidemia (Painter et al. 2005).

Support for the Brenner hypothesis came from observations by Keller et al., who found fewer

**Table 1** Intervention studies performed in pregnant rats to evaluate renal organogenesis and postnatal renal function in offspring

Author	Intervention	Outcome
Gilbert et al. (1991)	Late gestational exposition to gentamicin	Oligonephronia Early nephron compensatory adaptation Progressive glomerular sclerosis
Celsi et al. (1998)	Gestational exposition to dexamethasone	Oligonephronia Early nephron compensatory adaptation Arterial hypertension ↓ GFR Albuminuria ↓ Urinary sodium excretion rate and fractional sodium excretion ↑ Sodium tissue content
Lelièvre-Pégorier et al. (1998)	Gestational exposition to mild vitamin A deficiency	Oligonephronia
Vehaskari et al. (2001)	Gestational exposition to low-protein diets	Oligonephronia Apoptosis ↓ PRA ↑ Aldosterone Arterial hypertension
Woods et al. (2001)	Gestational exposition to low-protein diets	Glomerular enlargement ↓ Renal renin mRNA Arterial hypertension
Pham et al. (2003)	Uteroplacental insufficiency	Oligonephronia Apoptosis Arterial hypertension

nephrons at postmortem in individuals with essential hypertension (Keller et al. 2003). However, others have been unable to demonstrate a direct relationship between nephron number and hypertension or have found an inverse relationship between arterial pressure and nephron number in only certain racial groups (Hoy et al. 2006).

It has been shown that intrauterine growth restriction (IUGR) and factors that would be expected to limit fetal nutrition, such as maternal smoking and hypertension, can limit nephron endowment in humans (Hinchliffe et al. 1992). There is also evidence of reduced nephron endowment in severely disadvantaged populations, such as Aboriginal people living in remote parts of Australia, in whom there is an ongoing epidemic of hypertension and chronic kidney disease (Hoy et al. 2006). The balance of evidence indicates that the reduced nephron endowment in these Aboriginal populations is chiefly a product of macro- and micronutrient deficiency, although other factors, such as maternal smoking, diabetes, and infectious disease, also contribute (Hoy et al. 2006).

It appears that a nephron deficit does not necessarily lead to the development of adult hypertension, but a secondary insult, either phenotypic or environmental, might be required to initiate hypertension; the most probable candidates are high salt intake, age, and altered renin–angiotensin–aldosterone system function. Therefore, maternal malnutrition, leading to fetal reduced nephron endowment, when combined with excessive salt intake postnatally, might account, at least in part, for the unexpectedly high prevalence of hypertension in disadvantaged populations worldwide (Thrift et al. 2010).

Barker and colleagues' observations have extended the range of diseases associated with low birth weight to include atherosclerosis, coronary heart disease, type 2 diabetes mellitus, metabolic syndrome, stroke, and chronic bronchitis (Barker et al. 1989a, b, c, 1993a, b, 2002). These observations have been corroborated and extended by other epidemiologic studies and studies in twins (Uiterwaal et al. 1997; Barker et al. 2005; Kajantie et al. 2005; Lackland et al. 2000;

Keijzer-Veen et al. 2005; Bergvall et al. 2007; von Bonsdorff et al. 2016).

In a multi-ancestry genome-wide association study, meta-analysis of body weight in 153,781 individuals identified 60 loci where fetal genotype was associated with body weight ( $P < 5 \times 10^{-8}$ ). Overall, approximately 15% of variance in body weight was captured by assays of fetal genetic variation. Using genetic association alone, a strong inverse genetic correlation was found between body weight and systolic blood pressure, type 2 diabetes, and coronary artery disease. In addition, using large cohort datasets, it was demonstrated that genetic factors were the major contributor to the negative covariance between body weight and future cardiometabolic risk (Horikoshi et al. 2016).

The interest in this field has grown rapidly over the past decade. However, the most critical questions remain unanswered. Firstly, which of the children who have biochemical markers of metabolic disease will go on and develop overt metabolic disease in adult life? Secondly, what are the initiating events that trigger persistent metabolic programming? Thirdly, what are the mechanisms that lead to adverse programmed metabolic changes? (Cutfield et al. 2007). The low-birth-weight group includes those born small for gestational age (SGA), premature, or following in vitro fertilization, which is often associated with both SGA and prematurity. These three common childhood groups are likely to have been exposed to an adverse environment during different phases of early development and might endure future morbid consequences of this exposure. However, it is important to emphasize that associations of birth weight with adult disease outcomes have been found in studies which included term pregnancies and birth weight  $>2500$  g (Lurbe et al. 2001). In adults, the comparison of genome-wide DNA methylation profile, between Chronic Renal Insufficiency Cohort (CRIC) study participants, who had experienced rapid decline in kidney function and those with stable kidney function or improvement in kidney function, identified a set of epigenetic signatures in subjects with rapid decline in kidney function, including key genes NPHP4, IQSEC1, and TCF3, with established involvement in pathways known to promote the

epithelial to mesenchymal transition (Wing et al. 2014).

A list of selected epidemiological studies confirming the association of birth weight with different clinical outcomes along the human life cycle in developing countries and underprivileged populations is shown in Table 2 (Levitt et al. 1999; Law et al. 2001; Walker et al. 2001; Barros and Victora 1999; Nelson et al. 1998; Hoy et al. 1999; Bavdekar et al. 1999; Adair and Cole 2003).

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## The Future of Hypertension and Cardiovascular Disease in the Developing World

The survivors of an economic transition period are more likely to present the phenotype of lower birth weight coupled with either stunting or a higher body mass index in childhood or adulthood, which appears to be associated with the highest risks of morbid cardiovascular, renal, and metabolic outcomes into adulthood.

According to the WHO (WHO nutrition 2012), 30 million low-birth-weight babies are born annually (23.8% of all births). Although the global prevalence of such births is definitely dropping in the developed world, it is as high as 30% in many developing countries, frequently as a consequence of poor nutritional status and inadequate nutritional intake for women during pregnancy. As previously described, besides its negative impact on early development, low-birth-weight results in substantial costs to the health sector of developing countries, as its late consequence is a high burden of CVD morbidity and mortality affecting individuals at a younger age than observed in developed countries (Murray and Lopez 1994). The high prevalence of short stature in children of developing countries, a well-known sign of chronic malnutrition, is depicted in Fig. 3, showing high rates in important areas of the developing world [WHO *Global targets tracking tool*]. In 2015, an estimated one in four children globally (23.2% or 156 million children) is affected by stunting and is exposed to risks that include diminished cognitive and physical development (World Health Organization and World



**Table 2** Selected epidemiological studies investigating the association of birth weight and/or prematurity with clinical outcomes in developing countries and underprivileged populations

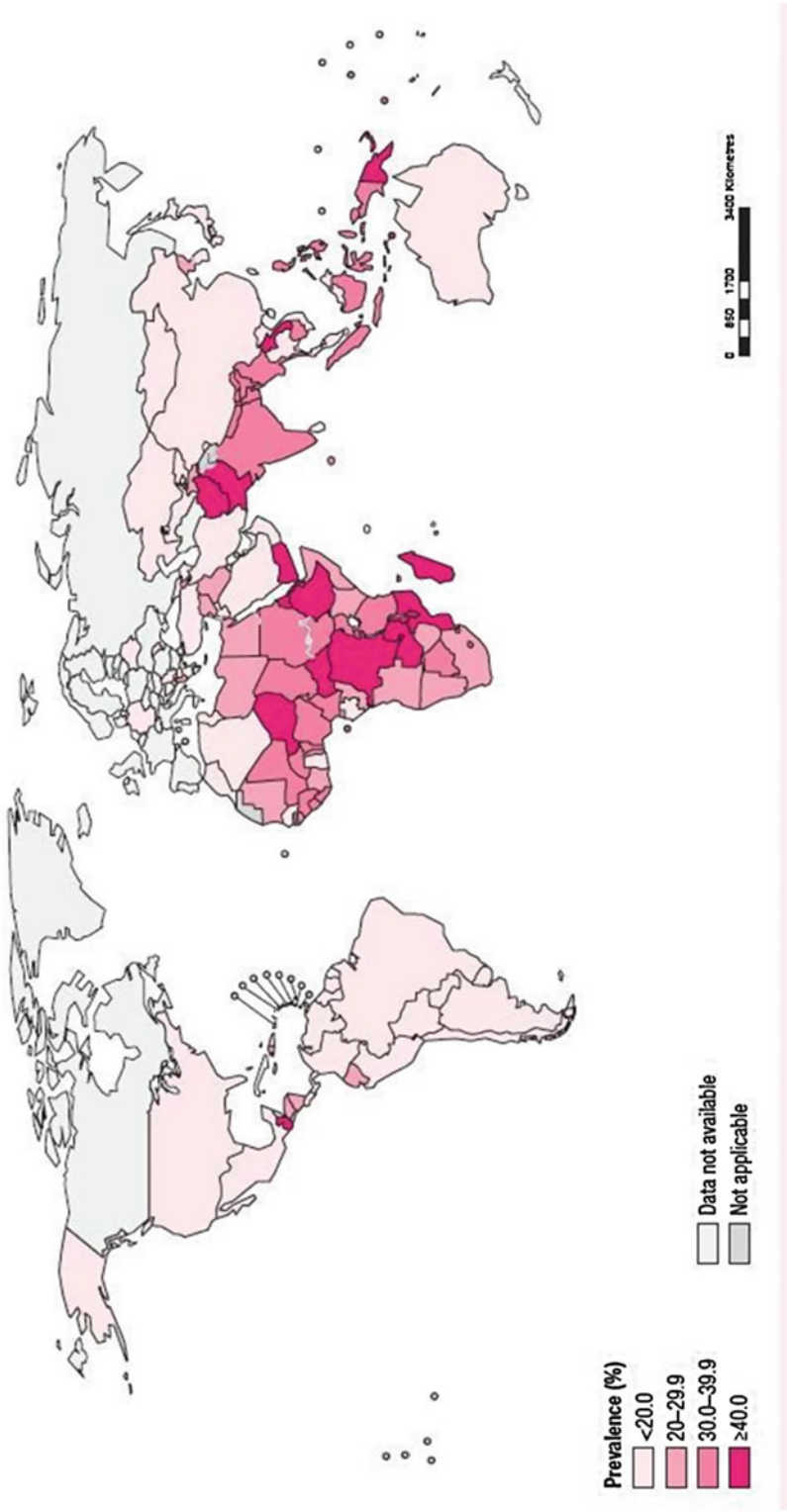
Author	Country	Population	Outcome	Aggravating influence
Levitt et al. (1999)	South Africa	5-year-old children	Inverse relation between BW and SBP	–
Law et al. (2001)	China, Guatemala, Chile, Sweden	3–6-year-old children Term pregnancy BW > 2.5 kg	Inverse relation between BW and BP	Current WT
Walker et al. (2001)	Jamaica	11–12-year-old children	Inverse relation between SBP and BW	Postnatal growth retardation Current WT
Barros and Victora (1999)	Brazil	14–15-year-old children	No association between BW and BP	Arterial hypertension more frequently diagnosed in adolescents born SGA
Nelson et al. (1998)	PIMA Indians (USA)	Adults Type 2 diabetics	Association of ↑ albuminuria with BW < 2.5 kg BW > 4.5 kg	
Hoy et al. (1999)	Australia (Aboriginals)	Adults	Inverse relation between BW and albuminuria	
Bavdekar et al. (1999)	India	8-year-old children	Inverse relation between BW and SBP Fasting plasma Insulin Plasma total and LDL cholesterol concentrations	Catch-up growth in previously growth-restricted children
Adair and Cole (2003)	Philippines	14–16-year-old children	Higher prevalence of elevated BP in low-BW males	Weight gain from late childhood into adolescence in males with low BW

Bank 2015). An estimated 93 million children under five (one in seven children globally) suffer from the negative effects of underweight, and 45% of child deaths are linked to undernutrition (World Health Organization and World Bank 2015).

An enormous task awaits developing countries, as national strategies to control the CVD epidemic must be developed and effectively implemented by individual countries, in parallel with new regional and global initiatives by international agencies concerned with health-care program facilitation, policy development, and research funding that are also required to strengthen and speed up these national efforts. It is of utmost importance that, along with vigorous efforts to optimize childhood growth, researchers and policymakers identify, quantify, and evaluate strategies to modify prenatal and perinatal determinants of adverse adult health outcomes.

Valuable initiatives can be found in WHO's "Working with individuals, families and communities to improve maternal and newborn health 2003" (WHO 2003) and the "Making Pregnancy Safer" program (WHO 2004) which emphasize the need for professional assistance during pregnancy in addition to provision of a balanced diet, a safe environment, and avoidance of tobacco use. These programs also emphasize the importance of breastfeeding during at least the first 6 months to ensure child health and survival. Breastfeeding is also important for provision of sufficient caloric intake for growth, without incurring in the dangers of overfeeding and higher weight gain in early childhood, which are associated with the use of nutrient-enriched formula and may predispose to hypertension and metabolic syndrome in later life (Singhal et al. 2001, 2003).

Schoolchildren and adolescents cannot be forgotten, it is mandatory to ensure their access to a



**Fig. 3** Prevalence of short stature in children younger than 5 years (Source: WHO Global targets tracking tool)

properly balanced nutrition and lifestyle orientation, which includes alcohol and tobacco avoidance, daily exercise, and weight control (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. 2011).

Optimal management of hypertension is important to prevent the risk of CVD and kidney disease. Assessment of estimated glomerular filtration rate, along with urine protein, preferably albumin, particularly in patients with hypertension, is important for the early detection of kidney disease. Aggressive treatment, particularly targeting systolic blood pressure, has been advocated (Bakris et al. 2009).

Unfortunately, low- and middle-income countries face many competing priorities for investment and end up committing less financial resources to health. As a consequence in poorer countries, most health-care costs must be paid by patients out of pocket. Thus, the cost of health care for NCDs creates significant strain on household budgets. Such costs can force families into catastrophic spending and impoverishment. Household spending on NCDs, and on the behavioral risk factors that cause them, translates into less money for necessities such as food and shelter and for the basic requirement for escaping poverty – education. Each year, an estimated 100 million people are pushed into poverty because they have to pay directly for health services. Economic analysis suggests that each 10% rise in NCDs is associated with a 0.5% reduction in the rate of annual economic growth. National health-care systems should undertake interventions for individuals who either already have NCDs or who are at high risk of developing them. Evidence from high-income countries shows that such interventions can be very effective and are also usually cost-effective or low in cost. When combined, population-wide and individual interventions may save millions of lives and considerably reduce human suffering from NCDs (WHO 2014, 2015). Accurate data from countries are vital to reverse the global rise in death and disability from NCDs, but a substantial proportion of countries have little usable mortality data and

weak surveillance systems, and data on NCDs are often not integrated into national health information systems. Improving country-level surveillance and monitoring must be a top priority in the fight against NCDs. In low-resource settings with limited capacity, viable and sustainable systems can be simple and still produce valuable data. The WHO STEPwise approach to Surveillance (STEPS) program is low cost and aimed at promoting CVD risk factor surveillance in developing countries [WHO Steps]. The WHO also provides information about costs and health effects at a regional level (CHOICE [ChOosing Interventions That Are Cost-Effective] project), with focus on management of systolic blood pressure and cholesterol (Murray et al. 2003).

Interventions to prevent NCDs on a population-wide basis are achievable and cost-effective, and the income level of a country or population is not a barrier to success. According to the WHO global status report on non-communicable diseases in 2014 [5], the “best buys” actions that should be undertaken immediately to produce accelerated results in terms of lives saved, diseases prevented, and heavy costs avoided are as follows:

- Protecting people from tobacco smoke and banning smoking in public places
- Warning about the dangers of tobacco use
- Enforcing bans on tobacco advertising, promotion, and sponsorship
- Raising taxes on tobacco
- Restricting access to retailed alcohol, enforcing bans on alcohol advertising, and raising taxes on alcohol
- Reducing salt intake and salt content of food
- Replacing trans fat in food with polyunsaturated fats
- Promoting public awareness about diet and physical activity, including through mass media
- Drug therapy (including glycemic control for diabetes mellitus and control of hypertension using a total risk approach) and counselling to individuals who have had a heart attack or stroke and to persons with high risk ( $\geq 30\%$ ) of a fatal and nonfatal cardiovascular event in the next 10 years

- Acetylsalicylic acid (aspirin) for acute myocardial infarction

Additional cost-effective and low-cost population-wide interventions that can reduce risk factors for NCDs include [5]:

- Nicotine dependence treatment
- Promoting adequate breastfeeding and complementary feeding
- Enforcing drink driving laws
- Restrictions on marketing of foods and beverages high in salt, fats, and sugar, especially to children
- Food taxes and subsidies to promote healthy diets

Although additional cost-effectiveness research is needed, there is strong evidence for the following additional interventions [5]:

- Healthy nutrition environments in schools
- Nutrition information and counseling in health-care national physical activity guidelines
- School-based physical activity programs for children
- Workplace programs for physical activity and healthy diets
- Community programs for physical activity and healthy diets
- Designing the built environment to promote physical activity

Evidence from high-income countries shows that a comprehensive focus on prevention and improved treatment following cardiovascular events can lead to dramatic declines in mortality rates. In a comprehensive literature review of journal articles published in English from January 2000 to May 2010, cost-effectiveness of interventions designed to reduce sodium intake was confirmed in the few available published studies (Wang and Labarthe 2011).

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## Conclusion

Coronary heart disease, stroke, type 2 diabetes, and other chronic diseases are not inevitable to human kind. They are the result of the changing pattern of human development. Many babies in

the womb in the Western world today are receiving unbalanced and inadequate diets. Many babies in the developing world are malnourished because their mothers are chronically malnourished. Protecting the nutrition and health of girls and young women should be the cornerstone of public health. Not only will this prevent chronic disease, but it will produce new generations who have better health and well-being through their lives. (Barker 2012)

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## Cross-References

- [Perinatal Programming of Arterial Pressure](#)

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## **Part IV**

# **Evaluation and Management of Pediatric Hypertension**



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## Abstract

The management of hypertension in the pediatric population begins with a thorough diagnostic evaluation which can be tailored to the individual patient based on age, symptoms, and severity of hypertension. We outline four phases of evaluation which are integral to the optimal management of hypertension in children. Phase 1 seeks to determine whether the patient is truly hypertensive in the nonmedical setting. This can be accomplished with either ambulatory blood pressure monitoring or self-monitored (home) blood pressure monitoring. Once hypertension is confirmed, the Phase 2 provides the initial screening for potential etiologies, hypertensive end-organ damage, and comorbidities. Phase 3 of evaluation further defines any abnormality identified during screening, and the Phase 4 determines the significance and remediability of the abnormality. By systematically using the four phases outlined in this chapter, the clinician can

conduct a comprehensive yet thoughtful evaluation of the hypertensive patient.

## Keywords

Secondary hypertension • Diagnosis • Evaluation • Etiology

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## Introduction

The successful treatment of children with hypertension begins with a thorough evaluation for the cause of elevated blood pressure (BP). Careful consideration must be given to the causative spectrum of hypertension in pediatric patients, which is broad and changes with age. The identification of a secondary cause of hypertension can give clues to the mechanism of the hypertension, potentially directing the choice of treatment.

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And in some cases, the secondary cause of hypertension may be amenable to a definitive cure (e.g., renal artery stenosis, pheochromocytoma).

Primary hypertension, also known as essential hypertension, has no clear cause and is presumed to be due to a confluence of factors, including genetic predisposition, obesity, dietary influences, and lack of exercise. Secondary hypertension, attributed to a specific disease process, is more common in children compared to adults. In children, especially infants, toddlers, and young children, a secondary cause should be assumed until proven otherwise and thoroughly sought out (Flynn et al. 2012). In older children with severe hypertension, a careful, comprehensive, and immediate evaluation for secondary causes is also required (NHBPEP 2004) (see Table 1). While the rule of thumb may be that secondary hypertension is most often diagnosed in the youngest and most severely hypertensive, there are always exceptions to the rule. Therefore, a thoughtful diagnostic evaluation in all children is important, as the cause may be remediable or may point to a preferred class of pharmacologic therapy.

The traditional pattern of a higher prevalence of secondary hypertension compared to primary hypertension in adolescence is changing with primary hypertension becoming increasingly evident during early adolescence and even late childhood. The primary factor responsible for the increase in prevalence of primary hypertension is *obesity*, now considered a global phenomenon associated with an increased risk for the development of cardiovascular and renal disease (Lurbe et al. 2001). Approximately 60% of obese adolescents (BMI  $\geq$  95th percentile) have at least one risk factor for future cardiovascular disease, including elevation of BP, abnormal lipids, and insulin resistance (May et al. 2012).

## Phases of Hypertension Evaluation

The diagnostic evaluation of hypertension follows a stepwise approach so that a comprehensive workup can be balanced with the minimization of unnecessary expensive and invasive diagnostic tests (see Table 2). The term “phase” of evaluation

**Table 1** Classification of hypertension in children ( $\geq 1$  year of age) and adolescents by casual office blood pressure measurements

Normal blood pressure	SBP and DBP less than the 90th percentile
Elevated blood pressure	SBP or DBP $\geq$ to the 90th percentile (or 120/80) but $<$ the 95th percentile, or 120–129/ $<$ 80 in teens $\geq 13$ years old
Stage 1 hypertension	SBP or DBP from 95th percentile to the 95th percentile + 11 mmHg, or 130–139/80–89 in teens $\leq 13$ years old
Stage 2 hypertension	SBP or DBP $\geq$ 95th percentile +12 mmHg, or $\geq 140/90$ in teens $\geq 13$ years old

Adapted from Flynn et al. (2017)

Percentiles refer to sex, age, and height appropriate norms  
Hypertension should be confirmed on at least 3 separate occasions

Patients should be characterized by the more severe classification if SBP and DBP differ

SBP systolic blood pressure, DBP diastolic blood pressure

is used in this text in an attempt to lessen confusion with the “stages” of hypertension defined in Table 1.

Phase 1: Is the patient truly hypertensive?

Confirmation of hypertension with ambulatory blood pressure monitoring (ABPM) or self-monitored blood pressure (SMBP)

Phase 2: Hypertension screening studies

- (A) Why does the patient have hypertension (etiology)?
- (B) What effects has hypertension had on the patient (end-organ damage)?
- (C) What other risk factors for cardiovascular/kidney disease does the patient have (comorbidities)?

Phase 3: Definition of abnormalities identified during screening

Phase 4: Determination of significance and correction of abnormality

### Phase 1: Is the Patient Truly Hypertensive?

Before a thorough evaluation for etiology is performed in a child with an elevated BP, confirmation that the hypertension is sustained should

**Table 2** Phases of hypertension evaluation

<b>Phase 1: Is the patient truly hypertensive in the nonmedical setting?</b>
Ambulatory BP monitoring
Self-measured (home) blood pressure monitoring
School-based blood pressure measurement
<b>Phase 2a: Screen for etiology</b>
Focused history and physical examination
Serum laboratory studies: electrolytes, BUN, creatinine, CBC
Urinalysis, urine culture
Renin and aldosterone profiling
Renal ultrasound with Doppler
Echocardiogram/EKG
<b>Phase 2b: Identification of end-organ damage</b>
Echocardiogram
Fundoscopy examination
Urine protein quantification
<b>Phase 2c: Screen for comorbidities</b>
Fasting insulin and glucose
Fasting cholesterol profiling (total serum cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides)
Polysomnography (if history suggests sleep disordered breathing)
<b>Phase 3: Definition of abnormalities</b>
Thyroid function
Catecholamine profiling
Renal imaging: VCUG, noninvasive renovascular imaging with CT or MR angiography
Abdominal imaging: CT or ultrasound
<b>Phase 4: Determination of significance and correction of abnormalities</b>
Renal arteriography (conventional or digital subtraction angiography)
Renal biopsy
MIBG scan
Renal vein renin collection

be obtained. Preferably three measurements should be taken in an upper extremity at least 2 min apart and the average of these compared to pediatric normative values at each measurement session. Accurate measurement of BP is dependent on a number of factors including the use of an appropriate-sized cuff. By example, increasing body weight is associated with an increase in arm circumference which accentuates the importance of recognizing the relationship

between arm circumference and BP cuff size and its impact on accurate BP measurement (Prineas et al. 2007). If an inappropriately small cuff is used, BP may be falsely overestimated. For a more detailed discussion regarding factors influencing blood pressure measurement in children see ► Chap. 13, “Methodology of Casual Blood Pressure Measurement” in the Part IV on “Assessment of Blood Pressure in Children: Measurement, Normative Data, Epidemiology.” Confirmation of BP elevation should be repeated on at least three separate occasions unless it is severe (Stage 2 hypertension) or the child is symptomatic. In the latter case, one should make immediate referral for evaluation and treatment.

Subsequently, confirmation of the elevated blood pressure outside of the clinical setting is essential to rule out white coat hypertension. This can be accomplished either through ABPM or SMBP. SMBP is typically performed at home and requires an appropriate-sized cuff and a BP monitor that has at a minimum been compared to the clinic monitor although monitors that have been independently validated in children are preferred. An in-depth discussion of home blood pressure monitoring can be found in Part II, “Assessment of Blood Pressure in Children: Measurement, Normative Data, and Epidemiology” of this textbook. School nurses can also be useful in collecting additional measurements. School BP equipment may not be well calibrated, and the nurse’s training may be variable; therefore, proper training of the nurses and monitor validation at local schools is time well spent.

### Role of ABPM

Since BP is not a static biologic parameter, assuming a single office BP measurement is representative of the patient’s true BP pattern may not be acceptable. Ambulatory BP monitoring, discussed at length in Part II, “Assessment of Blood Pressure in Children: Measurement, Normative Data, and Epidemiology” of this textbook, refers to the monitoring of BP using a device which is programmed to measure and record BP at frequent intervals, typically over a 24-h period in the ambulatory setting.

ABPM provides an assessment of BP load (the proportion of the day spent hypertensive) and allows for the diagnosis of white coat hypertension and masked hypertension. ABPM has a better ability to predict cardiovascular events and surrogate outcomes compared to office BP (Sorof et al. 2002; McNiece et al. 2007; Hermida et al. 2013; Eguchi et al. 2008).

In addition to the previously mentioned benefits, ABPM can help differentiate primary from secondary hypertension. Certain BP parameters that are measurable only with ABPM (BP load, nocturnal dipping, BP variability) have been associated with a secondary (primarily renal) cause of hypertension (Flynn 2002; Dursun et al. 2007; Patzer et al. 2003; Seeman et al. 2005; Dionne et al. 2008; Valent-Moric et al. 2012).

An algorithm for the evaluation of hypertension using different BP measurement techniques is described in Fig. 1. In the case where ABPM is unavailable, multiple office blood pressures or self-measured BP can be used.

## **Phase 2: Screening for Identifiable Causes, Comorbidities, and End-Organ Damage**

### **Why Does the Patient Have Hypertension?**

The most common etiologies of hypertension by age group are listed in Table 3. The exact percentages within each age group are unknown. While many adolescents will have primary hypertension, the percentage of secondary causes in this age group remains higher than in adults, and thus all pediatric patients must be screened for secondary causes.

### **Focused History and Physical Examination**

A thorough history is a key starting point for the assessment of childhood hypertension (Table 4). The newborn may appear to have sepsis, feeding disorders, or neurologic abnormalities, while older patients frequently are asymptomatic but may complain of nonspecific symptoms such as abdominal pain, epistaxis, chest pain, or headache. Children can have subtle abnormalities that

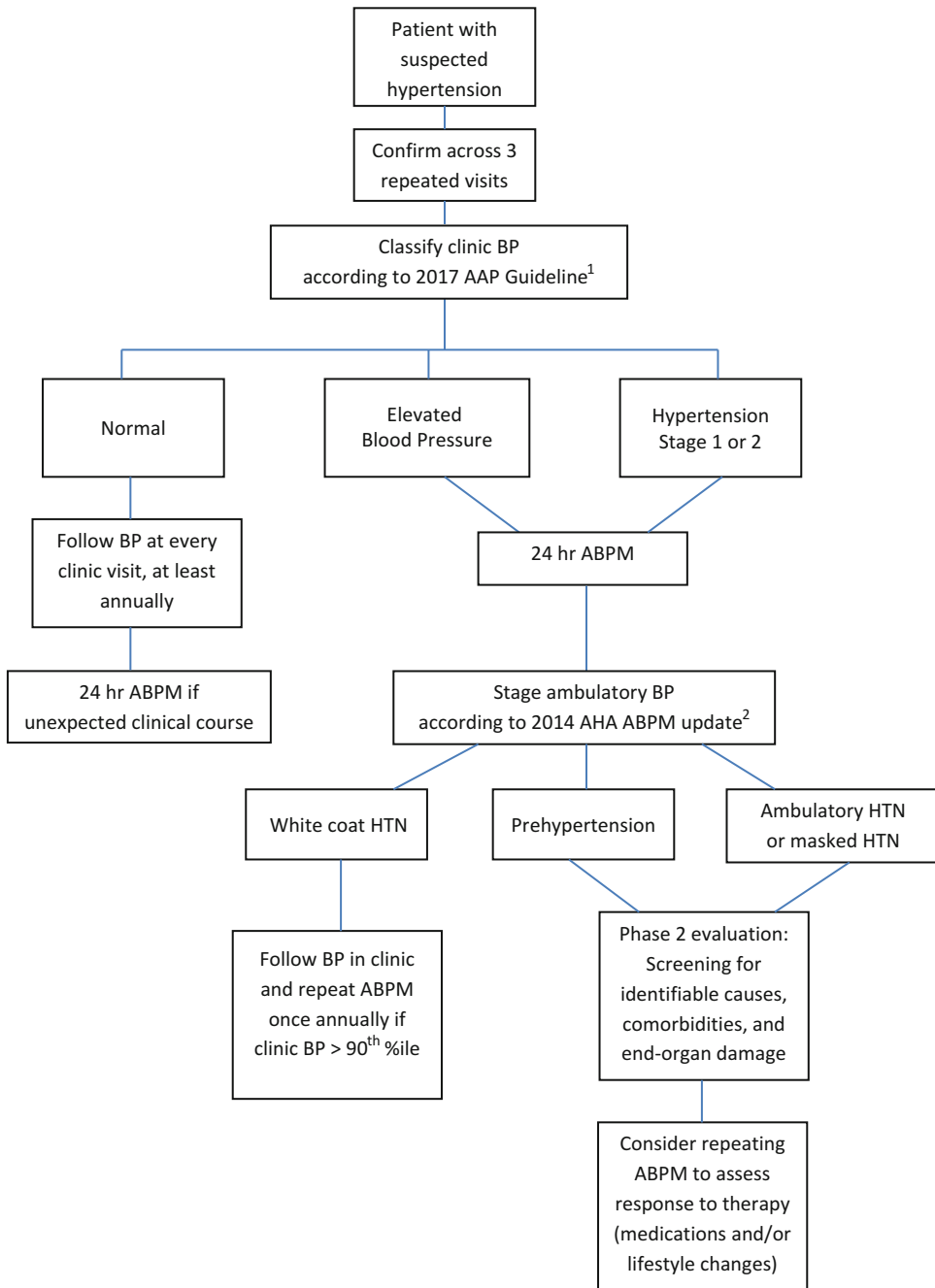
are difficult to attribute to hypertension such as personality changes, irritability, or changes in school performance.

The hypertension-oriented history should be directed at eliciting evidence of systemic diseases, use of medications including those which elevate BP (stimulant therapy for attention deficit and hyperactivity disorder, oral contraceptives, bronchodilators, cyclosporine or tacrolimus, corticosteroids, decongestants, performance-enhancing substances, caffeine, tobacco, and illicit drugs), congenital disorders, symptoms related to hypertension (headache, irritability), neonatal history (prematurity, low birth weight, use of umbilical catheters, neonatal asphyxia, or acute kidney injury), growth pattern, history of urinary tract infections, symptoms suggestive of an endocrine etiology (change in weight, sweating, flushing, fevers, palpitations, muscle cramps), sleep history (snoring, daytime somnolence), and family history of hypertension or other cardiovascular events.

The physical examination should be directed to detect causes of secondary hypertension (Table 5). In many children with hypertension, however, the physical examination will be normal. Initial evaluation should assess four extremity BP measurements to screen for coarctation of the aorta. Physical examination should also include calculation of the body mass index (BMI) because of the strong association between obesity and hypertension. Examination may reveal carotid or abdominal bruits, where stenotic lesions cause turbulent blood flow or asymmetric lower versus upper extremity pulses signifying a possible aortic coarctation. Evidence for secondary hypertension can also be supported by the finding on physical exam of hypertensive retinopathy, neurofibromas, café au lait spots, lesions of tuberous sclerosis, or thyromegaly.

### **Laboratory Testing**

The child with confirmed hypertension should be screened with laboratory testing to ascertain identifiable causes, comorbid conditions, and end-organ damage. A young child with Stage 2 hypertension or those with systemic symptoms should undergo a more extensive evaluation.



**Fig. 1** Suggested algorithm for the evaluation of hypertension using different BP measurement techniques (<sup>1</sup>Flynn et al. 2017; <sup>2</sup>Flynn et al. 2014)

On the other hand, the older or obese child with a significant family history of hypertension or other cardiovascular risks warrants a more streamlined approach. A serum creatinine and

estimation of glomerular filtration rate (GFR) [modified Schwartz formula] is fundamental (Schwartz et al. 2009). Serum electrolytes most commonly will be normal; however, alterations

**Table 3** Most common causes of hypertension by age group at initial presentation<sup>a</sup>

Age group	Etiology
Newborn	Bronchopulmonary dysplasia Coarctation of aorta or midaortic hypoplasia Congenital renal malformations Neurogenic tumor Renal artery stenosis Renal vessel thrombosis (artery or vein)
First year of life	Bronchopulmonary dysplasia Coarctation of aorta or midaortic hypoplasia Congenital renal malformations Iatrogenic (medication, volume overload) Neurogenic tumor Renal artery stenosis Renal parenchymal disease Renal vein thrombosis
Age 1–6 years	Central nervous system disorders Coarctation of aorta Endocrine disorders Neurogenic tumor Renal parenchymal disease Renal artery stenosis Vasculitis
Age 7–10 years	Coarctation of aorta Endocrine disorders Neurogenic tumor Primary hypertension Renal parenchymal disease Renal artery stenosis
Adolescence	Endocrine disorders Iatrogenic (medication) Illicit drug use (cocaine, PCP) Neurogenic tumor Primary hypertension Renal parenchymal disease Renal artery stenosis

<sup>a</sup>Not a comprehensive list and not in order of prevalence

of potassium concentrations can indicate primary or secondary hyperaldosteronism, particularly when the potassium is low and when there is a concomitant metabolic alkalosis. Liddle’s syndrome, the syndrome of apparent mineralocorticoid excess, glucocorticoid remediable aldosteronism, and other forms of monogenic hypertension are often associated with this electrolyte pattern and altered renin and aldosterone levels as summarized in Fig. 2 (Toka and Luft 2002). On the other hand, elevated potassium in

**Table 4** Relevant questions for the hypertensive history

Symptoms	Changes in weight (loss or gain), timeframe for weight change
	Flushing, diaphoresis, palpitations
	Headaches
	Psychiatric symptoms, or changes in school performance
	Syncope
	Sleep history (snoring, daytime somnolence)
Past medical history	History of unexplained fevers, especially in early childhood
	History of urinary tract infections
	Diagnosis with systemic diseases: systemic lupus erythematosus, polyarteritis, neurofibromatosis
Birth history	Gestational age at delivery, birth weight
	Bronchopulmonary dysplasia
	Use of umbilical artery catheters
	Neonatal asphyxia or acute kidney injury in neonatal period
Family history	Hypertension at a young age
	Endocrine disorders (thyroid and diabetes)
	Cardiovascular disease, especially early myocardial infarction or stroke
	Hypercholesterolemia
	Kidney failure, dialysis, or transplantation
Medications	Anti-inflammatory agents
	Oral contraceptives
	Decongestants
	Erythropoietin
	Anesthetic medication (ketamine)
	Stimulants: caffeine, methylphenidate, amphetamine, and dextroamphetamine
	Tricyclic antidepressants
	Immunosuppression: corticosteroids or calcineurin-inhibitors
	Illicit drug use

conjunction with a metabolic acidosis may suggest kidney disease or Gordon’s syndrome (pseudohypoaldosteronism type II). A decreased hemoglobin could suggest anemia due to chronic kidney disease.

The importance of a complete urinalysis with urinary protein or microalbumin and sterilely collected urine for culture cannot be overemphasized. Proteinuria or hematuria indicate possible glomerular disease or other non-glomerular conditions

**Table 5** Physical examination, clues to the etiology of hypertension

	Physical finding	Possible etiology
Body habitus	Underweight	Pheochromocytoma, hyperthyroidism, renal disease
	Overweight	Cushing's syndrome, primary hypertension
	Short stature	Renal disease
Skin	Cutaneous neurofibromas, café au lait spots, axillary freckling	Neurofibromatosis
	Tubers, ash leaf spots	Tuberous sclerosis
	Malar rash	Systemic lupus erythematosus
	Bruising, striae marks, acne	Cushing's syndrome
	Rashes	Vasculitis
	Needle tracks	Illicit drug use
Head	Unusual shape	Mass lesion
	Round facies (moon)	Cushing's syndrome
	Elfin facies	William's syndrome
	Proptosis	Hyperthyroidism
Neck	Goiter	Hyperthyroidism
Lungs	Rales, rhonchi	Heart failure
Heart	Rub	Pericarditis, uremia
	Murmur	Coarctation of aorta
Abdomen	Palpable mass	Wilm's tumor, neuroblastoma, severe hydronephrosis, polycystic kidney disease
	Hepatomegaly	Heart failure
	Hepatosplenomegaly	Congenital hepatic fibrosis associated with polycystic kidney disease
	Bruit	Renovascular disease
	Ascites	Renal disease
Back/flank	Bruit	Renovascular disease
	Flank tenderness	Pyelonephritis, obstruction, acute nephritis
Genitalia	Ambiguous or virilized	Congenital adrenal hyperplasia
Extremities	Diminished lower extremity pulses Leg BP >20 mmHg lower than arm BP	Coarctation of aorta
	Edema	Renal disease
	Bowed legs	Rickets associated with renal disease

such as pyelonephritis, obstructive uropathy, and interstitial nephritis. Additional testing can be tailored to the patient by positive findings in the individual and family history as well as physical exam.

### Imaging Studies

The renal ultrasound is a simple and informative noninvasive test and thus should be included in the initial screening. While the prevalence of abnormalities revealed by a renal ultrasound may be low, the importance of findings and noninvasive nature makes it a valued screening test. Ultrasound evidence of asymmetrically sized kidneys would

suggest renal dysplasia, reflux nephropathy, obstruction, or renal mass. Alternatively, symmetrically enlarged kidneys indicate potential infective (pyelonephritis), inflammatory, or glomerular disease. Additionally the renal ultrasound can identify calculi, nephrocalcinosis, parenchymal cysts, polycystic kidney disease, and multicystic dysplastic kidney. Doppler waveform analysis of the renal hilum can also provide information as to the patency of the vessels; however, its sensitivity for diagnosis of renal artery stenosis is limited, particularly in infants and children and in the detection of intrarenal lesions and incomplete stenoses in older children or adolescents (Olin et al. 1995; Brun et al. 1997).

	Inheritance Pattern	Age	K	PRA	Aldo	Aldo:PRA	GC resp	MR-A resp.	Rx	Gene	Gene Loci	Dx
Liddle's	AD	C,A	N or ↓	↓	↓		–	–	A, Tr	$\beta$ $\gamma$ subunit of ENaC	16p	
Gordon's	AD	A (C)	N or ↑	↓	N or ↑	↑	–	–	T	WNK1/4		
AME	AR	I,C,A	↓(N)	↓	↓		–	+	MR-A	11- $\beta$ -HSD	16q	
H-P	AD	C,A	N or ↓	↓	↓		–	reversed	A, Tr,T			
GRA/FH I	AD	I,C	N or ↓	↓	↑(N)	↑	+	+	G,A, Tr	Chimeric gene CYP11B1/CYP11B2	8q	18-hydroxy cortisol
FH II	AD	A	N or ↓	↓	↑	↑	–	+	MR-A/S,E		7p22	11 $\beta$ -hydroxylase
CAH	AR	I	N or ↓	↓	↓		–	+	MR-A	CYP11B1		
FGR	AR/AD	I	N or ↓	↓	↓		–	+	MR-A			

**Fig. 2** Monogenic forms of hypertension. *AME* apparent mineralocorticoid excess, *H-P* hypertension exacerbated by pregnancy, *GRA* glucocorticoid remediable aldosteronism, *FHII* familial hyperaldosteronism type II, *CAH* congenital adrenal hyperplasia with 11- or 17-hydroxylase deficiency, *FGR* familial glucocorticoid resistance, *AD* autosomal dominant, *AR* autosomal recessive, *Age* typical age at presentation, *I* infancy, *C* childhood, *A* adulthood,

*K* potassium, *N* normal, ↓ decreased, ↑ increased, *PRA* plasma renin activity, *Aldo* aldosterone, *Aldo:PRA* ratio of aldosterone to PRA (>30 diagnostic if Aldo. in ng/dl, PRA in ng/ml/h), *GC resp.* response to glucocorticoids, – negative, + positive, *MR-A resp.* response to mineralocorticoid receptor antagonists, *Rx* treatment, *A* amiloride, *Tr* triamterene, *T* thiazides, *E* eplerenone, *S* spironolactone (Adapted from Vehaskari 2009)

### Does the Patient Have Any Measureable Consequences of the Hypertension: End-Organ Damage?

The evaluation of hypertension is not solely to determine whether the measured level of BP exceeds some epidemiologically derived number but rather to ascertain the level at which it is associated with end-organ damage or cardiovascular outcomes. The evaluation of end-organ damage should include a complete assessment of the cardiovascular system (including blood vessels), kidneys, and nervous system. This assessment can assist in determining the chronicity and the severity of the hypertension.

Fundoscopic exam may reveal arteriolar narrowing, arteriovenous nicking, and more rarely hemorrhages, exudates, and optic disc edema. As few studies of retinal abnormalities have been conducted in hypertensive children, there has been no development of a standardized grading system for hypertensive retinopathy in children. In a cohort of 53 British children with severe hypertension, 18% were found to have hypertensive retinopathy, including findings of

retinal hemorrhages, exudates, and optic disc edema (Williams et al. 2013). Mitchell et al. examined children 6–8 years of age where for every 10 mmHg increase in systolic blood pressure, a narrowing of 1.93–2.08  $\mu$ m was seen in the retinal arterioles (Mitchell et al. 2007).

Left ventricular hypertrophy (LVH) is an independent risk factor for cardiovascular morbidity and mortality in adult patients. The echocardiogram is more sensitive than the electrocardiogram for the determination of left ventricular hypertrophy in children (Bratinscak et al. 2015). Left ventricular mass index values of >51 g/m<sup>2.7</sup> are associated with increased cardiovascular morbidity and mortality in adults (NHBPEP 2004), although values >95th percentile for age and gender have been proposed as a more appropriate cut-point for children (Khoury et al. 2009). ABPM has been shown to be a better predictor of left ventricular mass index compared to casual BP measurements (Sorof et al. 2002; Stergiou et al. 2011). Specifically, the best predictors include the 24-h wake or sleep mean BP, BP load, and BP index (McNiece et al. 2007). Additionally, carotid intimal-medial



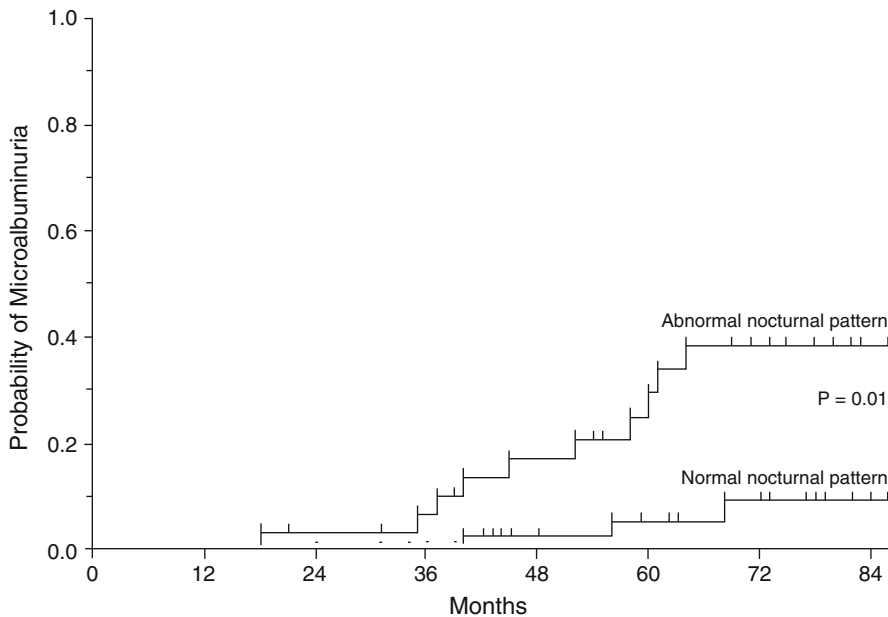
thickness has been shown to correlate with higher ambulatory blood pressure (Pall et al. 2010; Lande et al. 2006). Additional markers of end-organ damage include microalbuminuria (urinary albumin excretion rate of 20–200 micrograms/min in a timed urine collection or up to 300 mcg/mg creatinine in a spot urine collection), which is especially important in diabetics, patients with CKD, and the obese. Nocturnal hypertension has been shown to be associated with long-term progression of microalbuminuria in adolescents and young adults with diabetes (see Fig. 3) (Lurbe et al. 2002).

With regards to the association of ABPM with end-organ damage children, those with masked hypertension (normal office BP and elevated ambulatory BP) have similar prevalence rates of LVH as those with sustained hypertension (elevated office BP and elevated ambulatory BP), whereas those with white coat hypertension (elevated office BP and normal ambulatory BP) have LVH prevalence similar

to children with completely normal blood pressure (normal office BP and normal ambulatory BP) (McNiece et al. 2007). These findings have been shown in children with chronic kidney disease as well as in adolescents referred to a hypertension clinic (McNiece et al. 2007; Mitsnefes et al. 2010).

### What Other Comorbidities or Risk Factors for Cardiovascular Disease May be Present?

The major modifiable cardiovascular risk behaviors and risk factors are obesity, smoking, physical activity, healthy diet, dyslipidemia, hypertension, and diabetes (Steinberger et al. 2016). These risk factors should be screened for during the initial diagnostic evaluation after hypertension has been confirmed. A reasonable list of tests for cardiovascular risk assessment includes a fasting lipoprotein analysis including cholesterol,



**Fig. 3** Nocturnal blood pressure is associated with increased progression of microalbuminuria in diabetics (Lurbe et al. 2002). Increase in nocturnal blood pressure and progression to microalbuminuria Kaplan–Meier curves showing the probability of microalbuminuria according to the pattern of daytime and nighttime systolic

pressure. The probability of microalbuminuria differed significantly between the two groups ( $p = 0.01$  by the log-rank test; chi-square = 6.217 with 1 df). The risk of microalbuminuria was 70% lower in the subjects with a normal nocturnal pattern than in those with an abnormal nocturnal pattern

triglycerides, HDL, LDL, and VLDL, a fasting glucose and insulin for assessment of insulin resistance, and microalbumin excretion. However, not all of these studies have been endorsed by consensus organizations for routine screening.

Sleep-disordered breathing is associated with hypertension in children. If the history suggests a possibility of sleep apnea in a patient with hypertension, a referral for polysomnography should be undertaken.

### Phase 3: Define the Abnormality

Phase 3 of the evaluation is designed to further clarify and define abnormalities identified during the screening for etiology, end-organ damage, and risk factors in Phase 2. More extensive evaluation for an etiology as outlined in this section should be done for the very young hypertensive patient or for those with severe hypertension even if Phase 2 is unremarkable. These studies, however, do not need to be performed on all hypertensive children and adolescents.

During Phase 3, the aim is to identify the abnormality by specifically targeting the diagnostic tests to match the patient. For instance, if the patient by history and physical has stigmata of hyperthyroidism, e.g., weight loss, enlargement of the thyroid gland, or proptosis, a thyroid panel would be indicated. Individual consideration should be given to the measurement of plasma levels of various endocrine or vasoactive hormones as well as 24-h excretion rates of various hormones based on prior findings. Detection of proteinuria requires either quantification of protein excretion with the first morning urine using a urinary protein to creatinine ratio, or a 24-h urine collection for protein and creatinine (split into supine and upright fractions to assess for orthostatic proteinuria if indicated).

Further imaging studies may provide more details on the condition of the renal parenchyma and renovascular dysfunction. Radionuclide renal scanning can be very helpful as it can assess renal function, perfusion, obstruction, and presence of renal scarring. Radionuclide

scintigraphy to assess scarring may use either  $^{99m}\text{Tc}$  dimercaptosuccinic acid (DMSA),  $^{99m}\text{Tc}$  glucoheptonate (DTPA), or  $^{99m}\text{Tc}$  mercaptoacetyltriglycine (MAG3) and can be done with diuretics to help assess if an obstructive process is causing hydronephrosis. In children with a history of urinary tract infections and a concern for vesicoureteral reflux or bladder abnormalities, voiding cystourethrography should also be performed.

Renal ultrasound with Doppler measurements may result in a false negative, as it has poor detection of stenosis in small branches or accessory renal arteries. Other imaging studies are frequently necessary to rule out this etiology. Thus, if there is a high index of suspicion for renal artery disease, magnetic resonance angiography (MRA) and computed tomography angiography (CTA) are both appropriate for this indication. The choice of imaging modality is largely dependent on the institutional level of expertise available for each modality. Abnormalities of the mesenteric, splenic, and hepatic vessels often accompany renovascular disease in children. A certain percentage of these children may have neurofibromatosis type 1 (NF-1), abdominal coarctation, or intracranial disease (Glushien et al. 1953; Alpert et al. 1979; Becker et al. 1970; Wiggelinkhuizen and Cremin 1978). Genetic testing may be appropriate for some individuals to identify underlying mutations.

If other risk factors are identified, testing or appropriate referral should be performed. For example, elevated fasting glucose should be further evaluated with assessment of glycosylated hemoglobin (HgbA1c), glucose tolerance testing, and referral to endocrinology as appropriate. Quantification of proteinuria detected on urine dipstick should be performed with either a urinary protein:creatinine ratio performed on a first morning void or a 24-h urine sample. Referral to a nephrologist is indicated if this abnormal. Elevated serum lipoproteins in the obese could suggest dietary causes or rarely hypothyroidism. Familial forms of hyperlipidemia such as abnormalities in number or function of LDL receptors should also be assessed.

#### **Phase 4: Determination of Significance and Remediability of Identified Abnormalities**

The final phase of evaluation seeks to provide further information regarding a definitive medical or surgical cure for any identified abnormalities.

If a renal artery stenosis is detected by noninvasive renovascular imaging, invasive imaging should be pursued in order to better define the abnormality and possibly provide endovascular curative treatment. Catheter-based digital subtraction angiography is the gold standard for the evaluation of renovascular disease in children and should include imaging of the entire abdominal aorta and all of its branches, including the renal arteries. Renal vein renin sampling can be performed along with the angiography. Balloon angioplasty with or without stent placement can be curative to restore blood flow to the kidney but has shown variable response rates (Meyers et al. 2014).

The most sensitive and specific laboratory tests for pheochromocytoma are plasma metanephrines and normetanephrines (Havekes et al. 2009). If a neural crest tumor is suspected given severe or episodic hypertension and abnormal laboratory evaluation for catecholamines, then a  $^{123}\text{I}$ -metaiodobenzylguanidine (MIBG) scan would aid in localization for surgical correction and assessment of the extent of the disease. Genetic screening for a causative mutation should then be pursued, as it can be helpful in identifying treatment options, assessing the patient's risk for other types of cancers, and guiding the need for screening of other family members.

A finding of significant proteinuria or hematuria with red blood cell casts would suggest that a glomerular disease is present, and a renal biopsy would often be indicated to define the glomerular disease and guide the treatment plan.

Frequently, the information obtained during the hypertension evaluation is also helpful in guiding antihypertensive therapy. If abnormalities in serum electrolytes, renin, or aldosterone consistent with the genetic syndromes outlined in Fig. 2 are found, specific therapies such as amiloride and spironolactone are indicated

(Vehaskari 2009; Martinez-Aguayo and Fardella 2009). Additionally, in the presence of certain comorbidities such as chronic kidney disease or diabetes mellitus, the use of drugs affecting the renin-angiotensin-aldosterone system such as ACE inhibitors or angiotensin-receptor blockers is suggested.

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#### **Conclusion**

Primary hypertension, as defined by BP measurements exceeding the 95th percentile for age, height, and gender with no underlying cause, is increasing in prevalence, particularly in older children and adolescents with hypertension risk factors such as obesity. We recommend the evaluation of the pediatric hypertensive patient be performed in phases beginning with the confirmation of hypertension beyond office measurements (Phase 1). This confirmation should be followed by Phase 2 which includes a screening evaluation for (a) the etiology of the hypertension, (b) hypertensive end-organ damage, and (c) other risk factors for cardiovascular/kidney disease. Phase 3 further defines abnormalities identified during Phase 2, and Phase 4 determines the remediability of any observed findings.

As evidenced by the information presented throughout this text, much has been learned regarding the pathogenesis, diagnosis, and treatment of childhood hypertension in recent years; however, significant advances remain to be made. Evidence-based definitions for pediatric hypertension and indications for treatment are evolving. Our understanding of both pre- and postnatal causes of hypertension, the genetic determinants of hypertension, and the relationships between obesity, diabetes, and CKD on blood pressure regulation continues to grow. The value of more complex analyses of data captured by ABPM remains largely unexplored, and the most efficient tests and evaluation pathways for identifying secondary forms of hypertension and end-organ damage remain to be validated. Finally, data comparing treatment options for hypertension in children is sorely lacking.

## Cross-References

- ▶ [Ambulatory Blood Pressure Monitoring Methodology and Norms in Children](#)
- ▶ [Methodology and Applicability of Home Blood Pressure Monitoring in Children and Adolescents](#)
- ▶ [Methodology of Casual Blood Pressure Measurement](#)
- ▶ [Secondary Forms of Hypertension in Children: Overview](#)

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## Abstract

Data obtained from autopsy studies as well as noninvasive imaging techniques have demonstrated that end-organ changes occur in children and adolescents with mild to moderate elevations in blood pressure. These chronic elevations in blood pressure in pediatric patients induce changes in left atrial as well as left ventricular structure. The cardiac changes occur in parallel with alterations in the vascular system and subsequent development of atherosclerosis. Subclinical changes in renal function and microalbumin excretion are also noted in these patients. Mild to moderate elevations in blood pressure also impact cognitive functioning in children. The adverse effects of severe hypertension in children and adolescents on these organ systems are also well-known. Although additional longitudinal studies are required to elucidate the significance of these alterations, children with elevated blood pressures must be identified and treated appropriately in order to improve their long-term outcomes.

## Keywords

Hypertensive urgency • Left ventricular hypertrophy • Carotid intimal–medial thickness • Endothelial dysfunction • Microalbuminuria

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## Introduction

Primary hypertension in children and adolescents was generally thought to be an asymptomatic disease. However, mounting evidence confirms

that childhood hypertension is not without symptoms and target organ damage (TOD) occurs even in the early stages of hypertension. For example, children and adolescents with mild hypertension experience nonspecific symptoms that can impact school performance. Hypertensive children at initial evaluation are more likely to experience sleep disturbances and daytime fatigue than normotensive children. Moreover, 64% of hypertensive children are more likely to complain of nonspecific symptoms including headache, chest pain, and shortness of breath than normotensive children at initial evaluation (Croix and Feig 2006). Most important, treatment of hypertension significantly reduces the prevalence of these complaints 6 months following initiation of therapy highlighting the importance of screening and early recognition of childhood hypertension (Croix and Feig 2006). In addition to the symptoms described above that affect quality of life and school performance, hypertension in children and adolescents induces alterations in multiple organ systems with the potential for significant long-term morbidity as outlined below (Table 1).

**Table 1** End-organ changes in pediatric patients with chronic hypertension

Cardiac structure
Increased left atrial size
Left ventricular hypertrophy
Cardiac function
Diastolic dysfunction
Vascular structure
Atheromatous changes
Arterial stiffening
Endothelial dysfunction
Increased cIMT
Decreased cerebrovascular reactivity
Renal function
Microalbuminuria
Retinal vasculature
Arteriolar narrowing
Tortuosity
AV nicking
Cognition
Short-term memory
Attention/concentration
Learning disabilities

## Cardiac Structure

In the classical paradigm for the pathogenesis of hypertensive heart disease, development of left ventricular (LV) failure is preceded by alterations in both left atrial and ventricular geometry (Haider et al. 2003; Kostis et al. 1997; Kenchaiah and Pfeffer 2004). The changes in ventricular geometry occur in two different patterns (Kenchaiah and Pfeffer 2004). In concentric LV hypertrophy, parallel addition of sarcomeres causes an increase in the cross-sectional area and diameter of the cardiac myocytes (Lorell and Carabello 2000). These alterations lead to a significant increase in LV wall thickness out of proportion to an increase in size of the LV cavity (Lorell and Carabello 2000). In contrast, a symmetric increase in wall thickness as well as LV cavity size results in eccentric LVH as a result of sarcomere addition in series. In addition to left ventricular stress, numerous non-hemodynamic factors are thought to influence the development of altered left ventricular geometry including neurohormonal activation, biomarkers of inflammation, and hemostatic factors (Opie et al. 2006; Cohn et al. 2000; Drazner 2005; Bowman et al. 1997; Brull et al. 2001; Muscholl et al. 1998). Regardless of the mechanism, these alterations are thought to provide for normalization of afterload and preservation of systolic performance early in the development of hypertension (Cohn et al. 2000). However, as myocardial oxygen demand increases due to increased cardiac mass and persistently elevated wall stress, a decrease in coronary artery oxygen reserve is noted leading to increased apoptosis and cardiac cell death (Opie et al. 2006). Furthermore, abnormalities in myocardial electrical conduction in the hypertrophied muscle also trigger the development of arrhythmias.

## Atrial Structure

In terms of atrial structure, left atrial enlargement is associated with the duration of elevated blood pressure, the severity of systolic blood pressure, and pulse pressure in the general adult population (Benjamin et al. 1995; Gottdiener et al. 1997).

Although data are limited in the pediatric population, Daniels et al. (2002) studied a cohort of 112 pediatric patients with hypertension and found that 51% of patients had left atrial dimensions above the 95% upper confidence limit (Daniels et al. 2002). In statistical analysis, height, body mass index, and systolic blood pressure were independent predictors for left atrial enlargement (Daniels et al. 2002). Left ventricular geometry was also an independent predictor of left atrial size, and although the cross-sectional nature of this study prevented elucidation of cause and effect, the authors speculated that the hypertrophied left ventricle may demonstrate impaired diastolic filling necessitating increased left atrial volume (Daniels et al. 2002). The prognostic value of these findings in pediatric patients remains to be determined.

### Left Ventricular Structure and Function

In both adults and children, evaluation of echocardiographic left ventricular mass is the most well-studied tool for the evaluation of preclinical organ damage in the setting of hypertension. Several studies have suggested that the prevalence of left ventricular hypertrophy (LVH) in hypertensive adult patients range from 33% to 81% (Kannel et al. 1970; Pewsner et al. 2008). LVH has been found to be a risk factor for cardiovascular disease, cardiovascular morbidity, ventricular arrhythmias, and cardiovascular death (Levy et al. 1990; Verdecchia et al. 2001). Abnormalities in left ventricular structure are also present in up to 40% of children and adolescents with prehypertension and hypertension (Sorof et al. 2004; Litwin et al. 2006; McNiece et al. 2007; Brady et al. 2008; Kavey et al. 2007; Table 2). Urbina et al. measured several cardiovascular parameters including left ventricular mass and carotid intimal–medial thickness (cIMT) in normotensive, prehypertensive, and hypertensive adolescents (Urbina et al. 2011). The authors noted a gradual increase in LVM index in normotensive patients compared to both prehypertensive and hypertensive subjects (Urbina et al. 2011). Multivariate regression demonstrated that the presence of both prehypertension and hypertension

independently predicted changes in end organs as assessed by cIMT and left ventricular mass (Urbina et al. 2011). Using ambulatory blood pressure monitoring (ABPM), Richey et al. detected associations between development of LVH and systolic blood pressure as well as 24-h systolic blood pressure (SBP) load (Richey et al. 2008). In a follow-up study of children aged 7–18 years, subjects with LVH had higher ambulatory systolic blood pressures, diastolic blood pressures, and BMI (Richey et al. 2010). Patients with eccentric LVH demonstrated higher diastolic blood pressures (Richey et al. 2010). Sharma et al. recently demonstrated that nighttime SBP load and daytime SBP variability had a stronger association to LVMI compared to casual blood pressures highlighting the importance of ambulatory blood pressure monitoring in managing pediatric patients with hypertension (Sharma et al. 2013). A recent meta-analysis suggested that nighttime-time ambulatory blood pressure is also more closely associated with increased LVMI than daytime BP citing that ABPM provides more controlled conditions for measurement during sleep (Kollias et al. 2014). However, the associations between blood pressure elevations and LVH are not always consistent (Table 2). A separate study of 184 children who were referred for evaluation of hypertension at three centers demonstrated a prevalence of LVH of 41% at initial presentation (Brady et al. 2010). In this study, children with LVH were more likely to have a higher BMI and to be non-white compared to those without LVH. After controlling for age, sex, and height, no associations between blood pressure parameters at the initial visit and LVH were detected (Brady et al. 2010). A follow-up study of 49 hypertensive children found that only baseline BMI z-score was independently associated with change in left ventricular mass index (Brady et al. 2016). Together, these studies suggest that race and ethnicity in addition to BMI may influence cardiovascular risk in children with primary hypertension (Brady et al. 2010, 2016). In two studies, Litwin et al. and Sladowska-Kozłowska et al. analyzed LV geometry in 86 children following 1 year of antihypertensive therapy (Litwin et al. 2010; Sladowska-Kozłowska et al. 2011). In these studies, eccentric hypertrophy was the most common pattern of remodeling in patients



**Table 2** Prevalence and predictors of left ventricular hypertrophy in pediatric patients with essential hypertension

Reference	Population	Prevalence of LVH	Predictors of LMVI
Sorof et al. (2004)	32 patients aged 8–18	41%	Weight, BMI
Hanevold et al. (2004)	Review of pooled data with a mean age of 14	15.1%	BMI, ethnicity
Sorof et al. (2003)	97 children aged 8–18	37%	BMI z-score
Litwin et al. (2006)	72 patients aged 5–18	41.6%	Higher uric acid, higher birth weight
Kavey et al. (2007)	140 children with a mean age of 13	15%	Height, weight
Brady et al. (2008)	184 children aged 3–20	41%	Nonwhite, BMI z-score
Richey et al. (2008)	106 children aged 6–18	N/A	24-h systolic load, ABPM wake SBP, TEmax SBP
Assadi (2008)	174 children with a mean age of 15.3	36%	SBP, SBPi, BMI, CRP, microalbumin
Richey et al. (2010)	Children aged 7–18	38%	ABPPM SBP and DBP, BMI z-score
Brady et al. (2010)	184 children aged 3–20	49% African-American, 30% non-African-American	
Litwin et al. (2010)	86 children aged 5–17	46.5%	Waist circumference
Sladowska-Kozłowska et al. (2011)	86 children aged 5–17	46.5%	Waist circumference, TG/HDL
Urbina et al. (2011)	723 children	N/A	Prehypertension; hypertension
Bjelakovic et al. (2013)	67 children aged 12–17	38.8%	BMI
Sharma et al. (2013)	72 children aged 5–18		Nighttime SBP load and daytime SBP variability
Agu et al. (2014)	Case control of 46 hypertensive children aged 5–19	54%	
Brady et al. (2016)	49 children aged 3–22	53.1%	BMI z-score

with altered LV geometry (Litwin et al. 2010). These authors noted normalization of LV geometry following either non-pharmacologic or pharmacologic treatments (Litwin et al. 2010; Sladowska-Kozłowska et al. 2011). However, additional analysis demonstrated that measures of oxidative stress, waist circumference, and dyslipidemia were significantly associated with development of altered LV geometry in contrast to blood pressure measurements (Sladowska-Kozłowska et al. 2011). As a result, the authors suggested that the main determinant for improvement in end-organ changes was changes in body composition as opposed to blood pressure lowering itself. These findings highlight the complexity of the interaction between blood pressure, BMI, and inflammatory mediators in

inducing hypertensive-induced cardiac structural changes.

Some of the strongest data examining the childhood origins of left ventricular changes in childhood are derived from large-scale, longitudinal studies that have followed childhood cohorts into adulthood in Bogalusa, Louisiana; Muscatine, Iowa; Finland, and Australia which are now collaborating as the International Childhood Cardiovascular Cohort (i3C) Consortium (Dwyer et al. 2013). These studies have shown strong associations between cardiovascular risk factors such as hypertension and cardiac growth in childhood (Dwyer et al. 2013). More importantly, these studies have shown that the presence of these risk factors in childhood predicts adult left ventricular geometry (Dwyer et al. 2013). These results were

recently extended by Lai et al. in which the investigators examined the cumulative long-term effects of obesity and elevated blood pressure from childhood to adulthood (Lai et al. 2014). Using data from the Bogalusa Heart Study, these investigators estimated the long-term burden of body mass index and blood pressure using the area under the curve as a statistical model (Lai et al. 2014). In their study, the cumulative burden of body mass index and blood pressure in childhood predicted left ventricular hypertrophy in middle-aged adults (Lai et al. 2014). However, the relationship of body mass index–left ventricular hypertrophy was stronger than that of blood pressure–left ventricular hypertrophy (Lai et al. 2014). As mentioned previously, body mass index and blood pressures may have a different impact depending on race and ethnicity. Although the pathophysiological mechanisms are not fully understood, obesity and blood pressure are powerful predictors of left ventricular hypertrophy in adults, and these effects independently impact changes in cardiac structure beginning in early life (Lai et al. 2014).

In addition to LV structure, diastolic dysfunction is a well-recognized complication of hypertension in adults affecting up to 45% of patients even in the absence of LV hypertrophy (Fagard and Pardaens 2001). Similar findings have been reported in pediatric patients with hypertension (Snider et al. 1985; Johnson et al. 1999). Recently, Border et al. compared the ventricular function of 50 pediatric patients with primary hypertension to 53 normotensive, healthy controls (Border et al. 2007). In agreement with other reports, the authors did not detect any differences in markers of systolic function including shortening fraction, ejection fraction, or midwall shortening between the two groups (Border et al. 2007). However, when indices of both ventricular relaxation and compliance were measured using both M-mode and tissue Doppler echocardiography, significant differences between the two groups were observed (Border et al. 2007). When compared to the controls, 36% of hypertensive patients demonstrated abnormal left ventricular compliance primarily affecting those with concentric LVH (Border et al. 2007). Regression analysis revealed

that LV mass was the only significant predictor of LV compliance, whereas BMI predicted LV relaxation providing further evidence that compensatory changes in LV geometry could lead to maladaptive alterations in LV function (Border et al. 2007). These findings were recently extended by Agu et al. (2014). Using mitral valve annular spectral tissue Doppler imaging, the authors assessed diastolic impairment in 80 children with untreated primary hypertension who were otherwise healthy (Agu et al. 2014). The authors found decreased mitral annular E<sub>a</sub> and A<sub>a</sub> waves, a measure of ventricular relaxation, as well as increased E/E<sub>a</sub> ratio, a measure of ventricular compliance. Although these changes were subclinical, these indicate that subtle alterations in left ventricular function are present in patients with pediatric hypertension (Agu et al. 2014). Of note, systolic function has been found to be preserved in pediatric patients using M-mode shortening fraction, two-dimensional ejection fraction, as well as shortening at the mid-wall (Border et al. 2007; Agu et al. 2014).

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## Vascular Structure

In parallel with cardiac abnormalities, hypertension induces alterations in the structure and function of the arterial tree (Laurent and Boutouyrie 2007). The mechanisms underlying these changes are multifactorial and incompletely understood (Laurent and Boutouyrie 2007; Humphrey 2008). Increased pulse pressure in hypertension alters the orderly arrangement of elastic fibers within the media of the artery leading to fragmentation and an associated increase in both collagen and calcium deposition within the vascular wall (Humphrey 2008). Because elastin influences smooth muscle proliferation and migration, this redistribution of elastin fibers leads to dedifferentiation of smooth muscle cells and arterial wall hypertrophy (Duprez 2006). Mechanical stress also alters the activity of matrix metalloproteinases which are essential for maintenance of the extracellular matrix of the arterial wall (Laurent and Boutouyrie 2007). Continued wall stress enhances production of endothelin, a potent

vasoconstrictor which when combined with other inflammatory mediators contributes to significant endothelial dysfunction. Ultimately, these changes lead to structural reduction of the arterial lumen diameter and increased arterial stiffness (Laurent and Boutouyrie 2007).

### **Carotid Intimal–Medial Thickness**

To evaluate these alterations, vascular ultrasound has emerged as a noninvasive means to assess changes in vascular structure and risk of future cardiovascular events (Hodis et al. 1998). Specifically, altered carotid artery intimal–medial thickness (cIMT) has been demonstrated to be a surrogate marker for the presence and degree of atherosclerosis as well as for occurrence of future coronary events in adults (Hodis et al. 1998). In a study of 32 patients referred to a pediatric hypertension clinic, 28% of patients demonstrated increased cIMT (Sorof et al. 2003). Although associations with blood pressure parameters were not detected in their analysis, the presence of increased cIMT was significantly associated with the presence of LVH, suggesting a common pathway of cardiovascular adaptation to increased pressure and wall stress (Sorof et al. 2003). Similarly, in the Bogalusa Heart Study, office-based systolic and diastolic blood pressures in childhood did not predict cIMT in adulthood (Li et al. 2003). Lande et al. compared the cIMT results of 28 patients with newly diagnosed hypertension to 28 BMI-matched controls in an effort to control for the confounding effects of obesity on cIMT (Lande et al. 2006). These results demonstrated that cIMT was increased in hypertensive children relative to controls independent of BMI (Lande et al. 2006). Furthermore, a strong correlation was observed between cIMT- and several ABPM-based measurements including daytime systolic blood pressure load and daytime systolic blood pressure index (Lande et al. 2006). However, no assessment of metabolic factors such as lipid status was included in that study, so it is uncertain if the increased cIMT truly reflected atherosclerosis. Data from the Muscatine Offspring Study found that aortic intimal–medial thickness

in adolescents was associated with several cardiovascular risk factors including BMI, triglycerides, and systolic as well as diastolic blood pressure (Dawson et al. 2009). cIMT was associated with systolic blood pressure, pulse pressure, and BMI (Dawson et al. 2009). Therefore, these results highlight the complexity of the interaction between blood pressure, obesity, and dyslipidemia that leads to alterations in the vascular tree in childhood.

### **Pulse Wave Velocity**

In addition to cIMT, pulse wave velocity is a widely used noninvasive method to assess arterial stiffness (Lim and Lip 2008). In principle, a central pressure wave is generated upon left ventricular contraction during systole. The magnitude and speed of the pressure wave are influenced by multiple factors including left ventricular contraction, blood viscosity, and properties of the arterial tree. The wave advances until it encounters a branch point or other alterations in vascular structure. At that time, the wave is reflected back toward its origin. Physiologically, the reflected wave is important because early in diastole it augments coronary blood flow (Lim and Lip 2008). However, in the presence of non-compliant arteries, the reflected wave returns to central circulation during late systole increasing cardiac workload and decreasing the pressure support for coronary artery blood flow. Using this technology, elevations in childhood blood pressure consistently predicted arterial stiffening in adulthood in the Bogalusa Heart Study (Li et al. 2004). A recent report demonstrated that pulse wave velocity is increased in hypertensive adolescents compared to normotensive controls (Niboshi et al. 2006). In a separate report, elevated mean blood pressure independently predicted elevated pulse wave velocity in a larger cross-sectional study of over 200 adolescents (Im et al. 2007). A separate study of 138 patients found that 24-h SBP variability and daytime SBP variability were associated with altered pulse wave velocity and increased arterial stiffness (Stabouli et al. 2015).

## Autopsy Studies

These findings are also supported by autopsy studies. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study examined the role of various risk factors for development of atherosclerosis in 3000 accident victims aged 15–34 years who underwent autopsy (McGill et al. 1995). In their analysis, hypertension significantly augmented the risk for development of atherosclerosis in the cerebral arteries (McGill et al. 1995). In a separate follow-up study, hypertension also enhanced formation of raised lesions from fatty streaks in the abdominal aortas (McGill et al. 2000; McMahan et al. 2007). Interestingly, this association was only observed in African-American subjects and not in white subjects (McGill et al. 2000; McMahan et al. 2007). However, the PDAY Study used the intimal thickness of the renal arteries as a surrogate marker for blood pressure which may have confounded the association (McGill et al. 1995). In contrast, the Bogalusa Heart Study found that systolic and diastolic blood pressures in addition to several other traditional risk factors for cardiovascular disease were associated with development of fatty streaks and fibrous plaques in both the aorta and the coronary arteries (Newman et al. 1986). Together, these studies suggest that elevated blood pressure contributes to both initiation and progression of atherosclerosis.

## Endothelial Function

Another marker of vascular health is assessment of endothelial vasomotor responses by measuring brachial artery flow-mediated dilatation (FMD). In this assessment, the change in artery diameter in response to hyperemia is measured (Berenson et al. 1998). In adults, abnormal FMD or endothelial dysfunction is associated with development of increasing cIMT and left ventricular mass even in patients with prehypertension (Peretz et al. 2007; Juonala et al. 2004). Similar alterations in FMD were seen in pediatric patients with obesity, diabetes, as well as hypertension (Meyer et al. 2006). Lazdam et al. studied a group of normotensive

adolescents over 10 years who were noted to have persistent endothelial dysfunction (Lazdam et al. 2012). Individuals with low-normal FMD were noted to have statistically significant greater left ventricular mass, cIMT, and systolic blood pressure compared to controls over 10 years highlighting a potential connection between blood pressure, vascular health, and cardiac remodeling (Lazdam et al. 2012). In fact, early changes in endothelial functioning as well as arterial compliance were associated with development hypertension in a recent prospective analysis from the Framingham Offspring Study (Kaess et al. 2012). As a result, these arterial modifications may be precursors of hypertension as opposed to secondary complications (Kaess et al. 2012).

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## The Kidneys

Among adults, hypertension is the second leading cause of end-stage kidney disease in the United States. Data from the Multiple Risk Factor Intervention Trial demonstrated that even mild to moderate blood pressure elevations were associated with a decline in renal function over time (Walker et al. 1992). Despite its prevalence, the mechanisms through which mild, chronic elevations in blood pressure induce alterations in renal function are not completely understood, and histological examinations suggest that multiple molecular pathways may be involved in nephron loss (Hill 2008). Loss of renal autoregulation as a result of arterial stiffening, low-grade chronic inflammation, oxidative stress, and altered renin–angiotensin activity are all thought to contribute to renal dysfunction in the context of hypertension (Hill 2008). Although common in adults, children with elevated blood pressures typically do not demonstrate clinically apparent alterations in renal function. However, subtle alterations in renal function may be present. In adults, the presence of microalbuminuria is thought to be an early marker for hypertensive renal disease, and microalbuminuria is associated with increased risk of cardiovascular as well as all-cause mortality (Cirillo et al. 2000; Hillege

et al. 2002). Data in children and adolescents are limited. However, as part of the Bogalusa Heart Study, Hoq et al. demonstrated that elevated childhood blood pressure was associated with the development of microalbuminuria in young African-Americans (Hoq et al. 2002). Although not observed in white subjects, these observations suggest that even early hemodynamic alterations exert subtle alterations in renal function in the context of other specific genetic and environmental factors (Hoq et al. 2002). In agreement with these findings, Lubrano et al. assessed GFR and proteinuria in 146 children with prehypertension as well as 104 normotensive children. Relative to controls, a significant reduction in GFR was detected in patients with prehypertension (90 vs. 110 ml/min/1.73 m<sup>2</sup>) (Lubrano et al. 2009). Moreover, protein excretion was increased in patients with prehypertension (145 vs. 66 mg/m<sup>2</sup>/24 h) (Lubrano et al. 2009). Although the GFR and degree of proteinuria reported by the authors did not exceed values accepted as normal, these results suggested that mild elevations in blood pressure may induce subtle impairment in renal function (Lubrano et al. 2009). In a separate study, children with primary hypertension defined based on ABPM have been shown to have higher urinary albumin excretion compared to controls (Seeman et al. 2012). However, when evaluating 82 hypertensive children using ambulatory blood pressure monitoring, Conkar et al. did not detect any relationship between microalbuminuria and ABPM-based parameters (Conkar et al. 2015). In terms of cardiovascular complications, Assadi examined the relationship between left ventricular hypertrophy, microalbuminuria, and C-reactive protein (CRP) (Assadi 2008). In this study, estimated GFR, blood pressure, and left ventricular mass (LVM) were determined in 64 patients referred to pediatric nephrology clinic. The results demonstrated a correlation between blood pressure, LVH, and presence of microalbuminuria (Assadi 2008). In regression analysis, CRP, microalbuminuria, and systolic blood pressure were independent predictors of LVH (Assadi 2008). The author speculated that inflammation and microalbuminuria portend increased cardiovascular risk in pediatric patients

with hypertension (Assadi 2008). However, the applicability of these findings are limited due to the non-blinded, single-center study design.

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## The Retina

In a study of 800 hypertensive adult patients, the prevalence of early retinal vascular changes was 78% using direct ophthalmoscopy (Cuspidi et al. 2004). Several studies have also detected associations between development of hypertensive-induced retinal changes and other macrovascular complications of hypertension such as development of left ventricular hypertrophy and carotid artery stiffness (Porta et al. 2005). Several population-based studies have also suggested that individuals with retinal microvascular changes have increased cardiovascular morbidity and mortality (Liao et al. 1997). However, there have been few studies examining retinal alterations in pediatric patients with elevated blood pressures. A small case series of 21 infants with hypertension demonstrated that almost 50% of these patients had retinal microvascular alterations similar to those found in adults (Skalina et al. 1983). In a second study of 97 children with primary hypertension, the prevalence of arteriolar narrowing was 41%, tortuosity was 14%, and arteriovenous nicking was 8% (McGill et al. 1995). In a separate study, Daniels et al. examined the predictors of retinal vascular abnormalities in 50 pediatric patients with primary hypertension. In their analysis, diastolic blood pressure and a smaller rise in systolic blood pressure during exercise were independently associated with vascular anomalies (Daniels et al. 1991, 1993). In agreement with these findings, the Singapore Malay Eye Study reported strong associations between retinal arteriolar narrowing and blood pressure in young adults with hypertension (Sun et al. 2008). Mitchell et al. examined retinal arteriolar caliber in two cohorts of patients aged 6–8 and determined that each 10-mmHg increase in systolic blood pressure was associated with arteriolar narrowing by 2.08  $\mu$ m independent of body size, birth parameters, and age (Mitchell et al. 2007).

## Cognition

In adults, hypertension increases the risk of cerebrovascular disease and stroke. It is also associated with the development of subcortical and periventricular white matter lesions (Van Boxtel et al. 2006). Although the etiology of these lesions is unclear, several studies have suggested that elevated blood pressure impairs cognitive functioning in adults (Van Boxtel et al. 2006). Recently, the Maine–Syracuse Study examined the cognitive functioning of approximately 1500 patients using multiple domains on the Wechsler Adults Intelligence Scale (Robbins et al. 2005). Significant inverse associations between blood pressure parameters and cognitive functioning were observed including measures of psychomotor speed, concept formation, and abstract reasoning abilities (Robbins et al. 2005). Although limited by its cross-sectional design, these results indicated that hypertension is associated with poor performance in several aspects of cognition (Robbins et al. 2005).

As detailed elsewhere in this textbook, elevated systolic blood pressures but not diastolic blood pressures have been associated with impaired short-term memory, attention, and concentration in the pediatric age group (Lande et al. 2003). Hypertensive children have also demonstrated lower parental ratings of executive functioning in association with a higher rate of internalizing behaviors such as depression and social withdrawal (Lande et al. 2009). Adams et al. assessed the prevalence of learning disabilities in 100 children with hypertension compared to controls and found that children with hypertension had fourfold higher odds of having a learning disability with a prevalence of 28% (Adams et al. 2010). The physiologic basis of these neurocognitive deficits is poorly understood. However, hypertension has been associated with changes in cerebral vascular reactivity (Wong et al. 2011). In a study of 56 pediatric patients, cerebrovascular reactivity was measured in response to hypercapnia and was decreased relative to controls suggesting that increased vascular resistance and decreased compliance contribute to these cognitive changes (Wong et al. 2011). Because these studies have

been limited to analysis of databases and small numbers, a multicenter study to further explore the impact of childhood hypertension on the brain has been initiated (Lande et al. 2013).

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## Sequelae of Acute Hypertensive Crisis

### Central Nervous System

Central nervous system abnormalities are typically the most prevalent of end-organ complications in hypertensive crises in children (Adelman et al. 2000; Flynn and Tullus 2009). Cerebral autoregulation is responsible for maintaining constant cerebral blood flow despite alterations in blood pressure (Van Lieshout et al. 2003). However, as mean arterial pressure increases, disruption of the vascular endothelium and blood–brain barrier leads to fibrinoid deposition within the vascular lumen (Immick et al. 2004). The cerebral vasculature will dilate in an effort to improve perfusion, but these changes ultimately lead to edema and microhemorrhages primarily affecting the white matter in the parietal–occipital regions of the brain (Immick et al. 2004). As an imbalance between oxygen supply and demand develops, cerebral infarction can develop (Immick et al. 2004). In one case series of pediatric patients, visual symptoms were noted in 9% of children, seizures in 25%, encephalopathy in 25%, facial palsy in 12%, and hemiplegia in 8% (Zampagione et al. 1996). Although reversible with appropriate blood pressure control, prompt recognition is required to prevent long-term complications, especially the visual outcome of these patients as there have been reports of permanent decline in visual acuity following treatment of hypertensive crisis (Lee et al. 2008; Hulse et al. 1979; Browning et al. 2001; Logan et al. 1992). Browning et al. described four cases with vision impairment during an episode of malignant hypertension. Of the cases, two patients demonstrated normalization of visual acuity, whereas two patients with prolonged blood pressures of 220/180 had permanent impairment of visual acuity (Browning et al. 2001). In contrast, Logan et al. reported three

cases with permanent reductions in visual acuity despite normal-appearing optic discs (Logan et al. 1992). In terms of neurocognitive outcomes, Trompeter et al. found that outcomes were not significantly different when compared to a control group that consisted of children with chronic renal disease (Trompeter et al. 1982).

## Cardiovascular System

Cardiovascular complications are also common in severe hypertension (Flynn and Tullus 2009). Activation of the RAAS axis leads to an increase in systemic vascular resistance and increased myocardial oxygen demand as a result of increased left ventricular (LV) wall tension (Aggarwal and Khan 2006). In an attempt to compensate for increased LV tension, myocytes become hypertrophic (Nadar et al. 2005). In addition, enhanced deposition of extracellular matrix within the ventricle occurs further increasing the oxygen demand of the heart. Continued activation of the renin–angiotensin axis results in enhanced sodium absorption and increased total body water further worsening ventricular load (Aggarwal and Khan 2006). Because of increased metabolic demands, focal ischemia can develop impairing both left ventricular contraction and relaxation (Nadar et al. 2005). Ultimately, the left ventricle is unable to overcome the abrupt increase in systemic vascular resistance causing left ventricular failure and congestive heart failure (Frohlich 2004). In one case series involving adult and pediatric patients, heart failure was seen in 36% of patients, acute myocardial infarction was seen in 12% of patients, and aortic dissection was noted in 2% of patients (Zampaglione et al. 1996). It is important to emphasize that clinical findings of congestive heart failure are especially common in neonates with severe hypertension (Deal et al. 1992).

## The Kidneys

Acute kidney injury due to altered renal autoregulation and subsequent renal ischemia is also a complication of severe hypertension (Flynn and

Tullus 2009). Similar to the central nervous system, renal autoregulation provides for constant renal blood flow and glomerular filtration between mean arterial pressures of 80 and 160 mmHg. However, at extremes of arterial pressure, intraglomerular pressure will fluctuate directly with systemic pressure, and the afferent and efferent arterioles are unable to prevent alterations in glomerular filtration leading to ischemia and renal failure. Histological examination of renal biopsy specimens from patients with renal insufficiency secondary to malignant hypertension demonstrates an obliterative vasculopathy with fibrinoid necrosis and occasional thrombosis of interlobular arteries (Van den Born et al. 2005). The presence of thrombosis and microangiopathic hemolysis is thought to portend a poor prognosis (Guerin et al. 1988). In a study of 51 adult patients with malignant hypertension, 46 patients demonstrated renal insufficiency with 67% of patients presenting with a serum creatinine greater than 2.3 mg/dl (Gudbrandsson et al. 1979). More importantly, 30% of patients in the study remained on chronic hemodialysis (Gudbrandsson et al. 1979). In a study by Gudbrandsson, 50% of patients in hypertensive crisis presented with renal failure (Gill et al. 1976). In contrast to adults, data examining the prevalence of renal failure in pediatric patients with hypertensive crisis are limited. Several early case studies have suggested a prevalence of 50% with up to one-third of patients requiring renal replacement therapy (Kumar et al. 1996; Tanaka et al. 2003). Development of significant hematuria and proteinuria was also detected in these patients (Tanaka et al. 2003; Adelman and Russo 1981).

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## Conclusions

A preponderance of evidence demonstrates that alterations in end-organ structure and function occur early in the course of pediatric hypertension. Ongoing longitudinal studies are required to completely understand the significance of these findings in the pediatric population. However, similar end-organ changes in the adult population portend poor cardiovascular morbidity and mortality. Therefore, prompt recognition and treatment of

hypertension in the pediatric population is imperative to minimize the cardiac, renal, retinal, and cognitive complications in this patient population. But more importantly, these studies highlight the importance of defining appropriate blood pressure targets in the pediatric population to improve the long-term outcomes in children and adolescents with hypertension.

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## Cross-References

- ▶ [Cognitive and Behavioral Aspects of Childhood Hypertension](#)
- ▶ [Endothelial Dysfunction and Vascular Remodeling in Hypertension](#)
- ▶ [Epidemiology of Cardiovascular Disease in Children](#)
- ▶ [The Role of ABPM in Evaluation of Hypertensive Target-Organ Damage](#)
- ▶ [Vascular and Cardiac Imaging Techniques and Their Applicability to Childhood Hypertension](#)

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# Vascular and Cardiac Imaging Techniques and Their Applicability to Childhood Hypertension

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Elaine M. Urbina

## Abstract

Hypertension-related cardiovascular (CV) disease is a major cause of death in adults throughout the world. Subclinical measures of target organ damage (TOD) including left ventricular hypertrophy, increased carotid intima-media thickness, and elevated arterial stiffness can be measured in middle age and are predictive of later CV events. It has now been shown that high BP-related TOD abnormalities can be found in adolescents and young adults. In this review, we will discuss vascular and cardiac techniques to measure TOD in youth and the evidence linking blood pressure levels to abnormalities in structure and function of the CV system.

## Keywords

Pediatric • Hypertension • Left Ventricular Mass • Carotid Artery • Arterial Stiffness

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## Introduction

Among potentially modifiable health risk factors such as obesity and dyslipidemia, hypertension (HTN) is the leading cause of death in women and the second leading cause of death in men, behind smoking (Mozaffarian et al. 2016). Fortunately, early measures of target organ damage (TOD) such as left ventricular mass (LVM), carotid intima-media thickness (cIMT), and arterial stiffness can be evaluated to identify the highest risk individuals who require intensive blood pressure (BP) control (de Simone et al. 1995; O’Leary et al. 1999; Mitchell et al. 2010). This is critical since risk for CV events increases in a linear fashion across levels of BP without a clear cut-point for which levels of BP are “safe” (Nilsson 2012). These noninvasive measures are now being employed to evaluate risk in pediatric patients (Urbina et al. 2009). In this review, we will discuss the techniques of measurement of

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TOD in youth and the evidence relating BP levels in young patients to vascular and cardiac damage.

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## Rationale for Measuring CV Function in Youth

Ischemic heart disease and stroke were the leading causes of death in the world in 2012 ([World Health Organization](#)). By 2030, 40.5% of the US population is projected to have CV disease (CVD) ([Roger et al. 2012](#)). Many of these cases of CVD are due to HTN and by 2030, 41.4% of the US population is predicted to have HTN, an increase of 8.4% from previous estimates ([Mozaffarian et al. 2016](#)). Although the prevalence of HTN in children is much lower, 11% of youth in the USA have either pre- or sustained HTN ([Kit et al. 2015](#)) with an increase seen from the late 1980s to early 2000s coincident with the onset of the obesity epidemic. Since autopsy studies in adolescents with hypertension show BP levels are associated with increased atherosclerosis ([Tracy et al. 1995](#)), attention to diagnosis of HTN and evaluation of subsequent BP-related TOD in youth is critical to prevent future CV events.

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## Measures of CV Structure and Function and their Relationship to BP Levels in Children

A comprehensive CV assessment includes measures of CV structure, such as left ventricular mass (LVM) and carotid intima-media thickness (cIMT) along with measures of function including cardiac systolic and diastolic function and assessment of arterial stiffness and vascular endothelial function. Since these tests measure different properties of the CV system and are influenced by different risk factors, CV assessment should include a combination of techniques.

### Vascular Structure

Ultrasound of the carotid artery is the most commonly performed measure of vascular structure as it is straightforward to assess and relates to CV events in adults ([O'Leary et al. 1992](#)). The combined

thickness of the intima and media is reported because ultrasound does not allow for separation of the two arterial layers since changes of the gain settings on the device will alter location of the intima/media border. Techniques in development may overcome this limitation ([Peters et al. 2013](#)). The femoral artery can also be evaluated but offers little advantage as it is more difficult to image and correlates strongly with cIMT ([Rietzschel et al. 2001](#)). The abdominal aortic thickness may be the earliest reflection of atherosclerosis ([Dawson et al. 2009](#)) but imaging requires additional equipment (curved array transducer) and the testing protocol may be less acceptable to patients as these studies must be performed in the fasting state ([Jarvisalo et al. 2001](#)).

Early data from the 1990s demonstrated that BP levels measured as young as 9 years of age predicted higher cIMT as a young adult ([Juonala et al. 2010](#)). Later studies measured cIMT in adolescence and found BP was an important correlate of carotid thickness ([Sanchez 2000](#); [Jourdan et al. 2005](#)). Although youth with sustained HTN have the highest cIMT ([Meng et al. 2015](#); [Kollias et al. 2014](#)) youth with less severe elevation in BP (>90th%) also have cIMT thickening ([Urbina et al. 2011a](#); [Kollias et al. 2013](#)). The addition of other risk factors including obesity and dyslipidemia appears to increase the risk for carotid atherosclerosis above that expected with isolated HTN ([Stabouli et al. 2005](#); [Sorof et al. 2003](#); [Elkiran et al. 2013](#)). And, the degree of BP elevation is also important. [Lande et al. \(2006\)](#) found that cIMT thickness was correlated with daytime SBP index, an indication of HTN severity measured by 24 h ambulatory BP monitoring (ABPM). Thicker cIMT has also been reported in youth with type 1 diabetes mellitus and reduced nocturnal BP dipping ([Lee et al. 2011](#)). Finally, children with chronic kidney disease also have accelerated carotid thickening ([Mitsnefes et al. 2005](#)) with children on dialysis demonstrating higher cIMT than patients with milder chronic renal insufficiency.

### Arterial Stiffness

Recognizing that the arterial wall behaves somewhat like an elastic solid, but also as a viscous liquid ([Nichols 2005](#)), has led biomedical

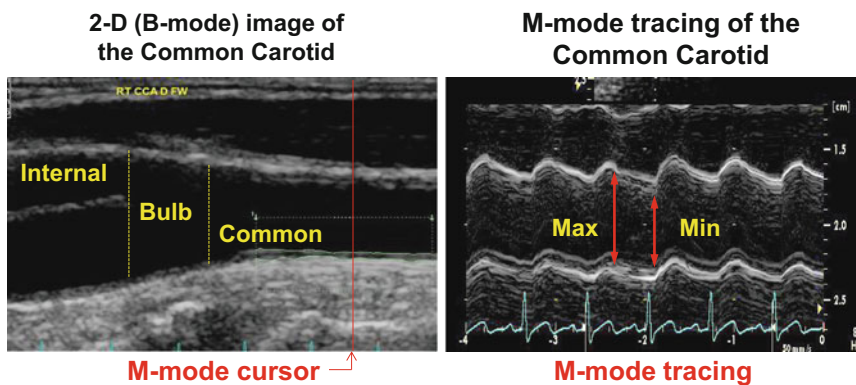
engineers to develop a variety of techniques to assess arterial stiffness – each with their own strengths and weaknesses. Regardless of technique, the importance of measuring arterial stiffness is seen in Framingham Heart Study data showing that a pulse wave velocity (PWV)  $\geq 11.8$  m/sec is associated with a nearly 50% increase in risk for a CV event over a short (7.8 years) follow-up period (Mitchell et al. 2010). Increased arterial stiffness may actually precede the development of HTN, rather than be caused by it (Liao et al. 1999).

Carotid stiffness can be obtained using the “M-mode” feature of the standard ultrasound machine during imaging for measurement of the common carotid artery. The maximal (systolic) and minimal (diastolic) common carotid diameters are obtained for calculation of carotid stiffness (Fig. 1). Different aspects of carotid stiffness are evaluated using a variety of calculations (Urbina et al. 2009). Data from adolescents with newly diagnosed HTN (mean age 15 years) demonstrated stiffer carotid arteries (higher elastic modulus and beta stiffness index) compared to normotensive controls (Litwin et al. 2004). Similar to cIMT, increased carotid stiffness is also found in prehypertensive youth well before progression to sustained HTN (Urbina et al. 2011a). Severity of renal disease is also important since children on dialysis have the highest carotid stiffness as compared to subjects with mild CKD or normal age-matched controls (Mitsnefes et al. 2005). However, youth with even mild CKD

may develop increased carotid stiffness if there BP control is suboptimal (BP >75th%) (Sinha et al. 2015). Unfortunately, after renal transplant, abnormalities in carotid stiffness do not improve likely related to inadequate 24 h BP control (Mitsnefes et al. 2004).

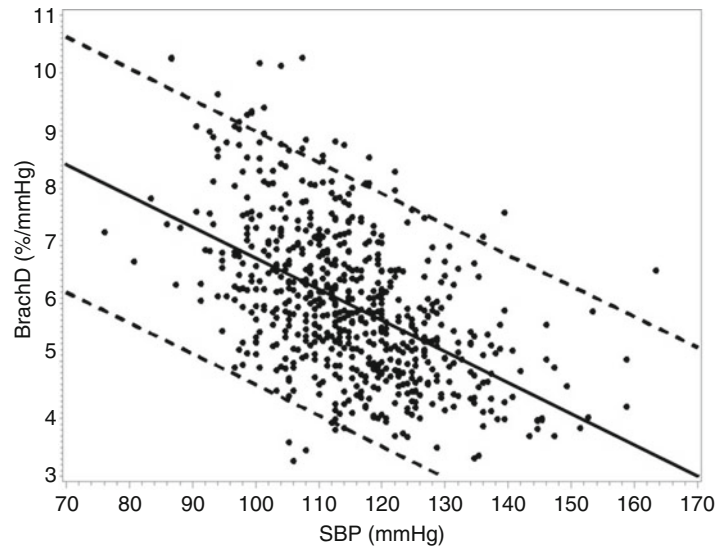
Other ultrasound methods to evaluate arterial stiffness have also been developed including radio frequency wall-tracker devices (“A-mode”), but these are less readily available. However, the A-mode technique was useful in demonstrating a curvilinear decline in brachial artery distensibility with increasing DBP in a large cohort of adolescents (Whincup et al. 2005). Arterial stiffness can also be measured with nonultrasound based devices. A cuff-based pressure device that measures resting brachial artery distensibility is available that is similar to the A-mode ultrasound technique and has also demonstrated a fall in brachial distensibility across the BP distribution (Fig. 2) (Urbina et al. 2011a).

PWV is a widely available technique to measure arterial stiffness. It measures the speed by which the pulse ejected by the heart propagates along the arterial tree. Tonometric devices are commonly used where pressure sensors are placed on a proximal (usually carotid) and then distal (usually femoral) artery. PWV has been shown to be elevated (indicating a stiffer vessel) in a variety of pediatric diseases including obesity-related insulin resistance (Urbina et al. 2012) type 1 (Urbina et al. 2010a) and type 2 diabetes mellitus, (Urbina et al. 2010b) acute post-streptococcus glomerulonephritis (Yu et al. 2011),



**Fig. 1** Carotid B-mode and M-mode ultrasound for measurement of carotid stiffness (Reproduced with permission, Urbina 2016)

**Fig. 2** Decline in brachial artery distensibility with increasing SBP (Urbina et al. 2011a).  $R^2 = 0.27$ ,  $p \leq 0.001$ ; solid line = mean, dotted lines = 95% confidence intervals (Reproduced with permission, Urbina 2016)

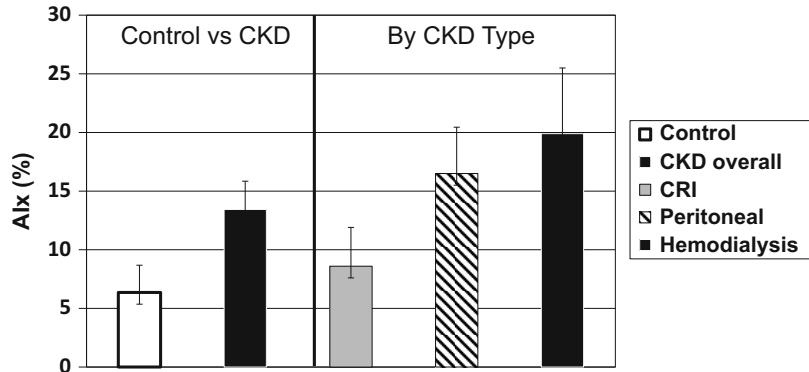


chronic kidney disease (Dursun et al. 2009), high brachial BP (Phillips et al. 2015), and high central (aortic) BP (Totaro et al. 2015). PWV is also elevated with prehypertension (Urbina et al. 2011a; Zhu et al. 2007) and this relationship remains true regardless of level of adiposity (Lurbe et al. 2012). Abnormal BP in response to exercise (Madueme et al. 2013) or on ABPM (Kenny et al. 2011) has also been associated with higher PWV after successful repair of coarctation of the aorta. BP variability is also important since 24 h SBP variability was found to be the only independent determinant of PWV in one study of children and adolescents referred to a HTN clinic (Stabouli et al. 2015). High risk youth who have undergone kidney (Briese et al. 2008) or heart transplantation (Klinge et al. 2009) or have systemic lupus erythematosus (Canpolat et al. 2013) also have higher PWV as compared to controls, with PWV correlating directly with BP levels. A cuff-based device to measure brachial-ankle PWV has also been used extensively in Asia where PWV was higher in adolescents with multiple CV risk factors (Miyai et al. 2009; Niboshi et al. 2006; Im et al. 2007) especially those with sustained HTN (Meng et al. 2015).

Augmentation index (AIx) is a vascular parameter related to arterial stiffness that incorporates features of wave reflections. It is also measured with pressure tonometry. Since the CV system is not an open-ended structure, boluses of blood

ejected by the heart are reflected back after impacting various branch points. Therefore, the true cardiac afterload, or force against which the heart must pump, is a summation of the outgoing and reflected waves (Patange et al. 2012). To measure AIx, a simulated aortic pressure curve, is calculated from the measured radial pressure curve with a “transfer function” validated in the catheterization lab (Nichols 2005). The outgoing and reflected waves are extracted from the simulated aortic pressure wave and AIx is calculated as the difference in pressure between the main outgoing cardiac pulse wave and the incoming reflected wave as a percentage of pulse pressure normalized to a heart rate of 75 beats per minute. Flexible vessels return the wave slowly arriving late in systole or early in diastole. Stiff vessels return it quickly arriving in early systole “augmenting” the central aortic pulse pressure. This increased pressure raises demand upon the heart and reduces the area under the curve of the pulse wave during diastole thereby lowering the driving pressure for coronary filling (Nichols 2005). An increase in oxygen demand and decreased blood supply to the coronary arteries is the pathophysiology behind the observation that a 10% increase in AIx resulted in a relative risk for total CV events of 1.318 (95% CI 1.093-1.588) in a large meta-analysis of adults studies (Vlachopoulos et al. 2010). In youth, increased

**Fig. 3** Elevated AIx in Children with CKD. N = 62, mean age 15 years (Patange et al. 2012) (Reproduced with permission, Urbina 2016)



AIx has been found with both HTN and prehypertension (Urbina et al. 2011a). In children with CKD, AIx is highest in patients on hemodialysis followed by patients on peritoneal dialysis who still have stiffer vessels than healthy youth (Fig. 3) (Patange et al. 2012).

## Endothelial Function

Arterial function measures the viscoelastic properties of the arterial wall (Nichols 2005), an entirely different parameter than endothelial function which represents the ability of the endothelium to respond to stress by releasing nitric oxide. The most established method for measurement of endothelial function uses ultrasound of the brachial artery for flow-mediated dilation (FMD). Similar to other vascular measures, FMD has been linked to hard CV events in adults with clustered metabolic syndrome risk factors (Suzuki et al. 2008). Brachial FMD is challenging to measure reproducibly, requires precise training and rigorous quality controls, and may not be feasible in younger children due to the discomfort of inflating a BP cuff on the forearm for 5 min to induce the ischemic stimulus (Urbina et al. 2009). Therefore, fewer pediatric data are available and most applied the technique to youth with significant concomitant illness. For instance, children with chronic renal failure had lower FMD compared to age-matched controls (Kari et al. 1997) with a graded decrease in endothelial function related to severity of renal impairment (Tawadrous et al. 2012). FMD appears to be acutely impaired directly after dialysis possibly due

to increased sympathetic nervous system outflow in response to a decreased effective circulating volume (Lilien et al. 2005). No studies have systematically measured FMD in pediatric HTN. However, one study of school aged children found that FMD was negatively correlated with mean 24 h ambulatory SBP and DBP (Aggoun et al. 2008).

There are also nonultrasound methods for measurement of endothelial function. One device (EndoPAT, Itamar Medical, Caesarea, Israel) uses a technique called peripheral artery tonometry to measure reactive hyperemic index (RHI). Finger cuffs are placed on the control and test arm, where the BP cuff is inflated. After 5 min of occlusion, the cuff is released and the device measures RHI, a parameter related to FMD (Kuvin et al. 2003). One study evaluated RHI in drug-naïve adults with HTN. In multivariable models, only a weak relationship was found between SBP and RHI after adjustment for other variables (Yang et al. 2011). However, no controls were studied so it is not clear if RHI differs between normotensive and hypertensive subjects. No systematic studies of RHI in youth with HTN have been conducted.

Laser Flow Doppler (LFD) is another technique to measure endothelial function. Although a LFD occlusion protocol has been developed, a heating stimulus can also be used that may be better tolerated in younger children who may not sit still through the 5 min of cuff inflation needed to induce an ischemic stimulus. Although the device measures microvascular response which relates to but is distinct from endothelial function of medium



muscular vessels like the brachial artery, adult studies have found reduced hyperemia in response to local heating with hypertension (Lindstedt et al. 2006). Pediatric patients with primary hypertension have not been studied but youth with type 1 diabetes and elevated BP had lower LFD compared to controls (Khan et al. 2000) suggesting the usefulness of LFD as an endothelial function measure in pediatric diseases.

The oldest method for measurement of endothelial function is venous plethysmography. A stretchy “strain gauge” is strapped around the mid forearm, and BP cuffs are inflated to near DBP on the upper arm and the wrist. This results in obstruction of venous outflow with normal arterial inflow. Thus, the increase in limb volume (circumference) is proportional to the rate of arterial inflow. The volume change is recorded in electrical resistance units. An advantage to this technique is that one can avoid the confounding effect of systemic counterregulatory systems (such as an increase in HR with administration of peripheral vasodilators) by confining the study to one limb. Mechanistic studies can also be performed by infusing specific agonists/antagonists but invasive microdialysis catheters are required. A disadvantage is that the technique only evaluates resistance vessels, not the conduit vessels (like the aorta) where the first development of atherosclerosis likely occurs (Barac et al. 2007). A few pediatric studies have been conducted using this technique but one study of 10-year-old children evaluated forearm blood flow during handgrip and mental stress testing. They found that BP response during stress tests was exaggerated in the obese as compared to lean youth (Ribeiro et al. 2005).

## Cardiac Structure

Echocardiography, first described in 1953 (Singh and Goyal 2007) is the most widely accepted imaging modality for evaluation of BP-related TOD in both adults (Marwick et al. 2015) and children (Expert Panel on Integrated Guidelines for Cardiovascular H, Risk Reduction in C, Adolescents and National Heart L and Blood I 2011).

Left ventricular hypertrophy (LVH) is a robust marker of CV risk since left ventricular mass (LVM) above  $51 \text{ g/m}^{2.7}$  predicts hard CV events in adults (de Simone et al. 1995). Calculation of LVM is performed by a variety of methods including M-mode which provides thickness of the intraventricular septum, LV chamber, and posterior wall in diastole; 2D which assumes an elliptical shape of the LV cavity and LV muscle; and more advanced 3D methods (Marwick et al. 2015) which may correct some of the weaknesses in the earlier methods but is not as readily available. Since a larger individual needs a larger heart, the raw LVM must be indexed to body size. There remains controversy as to the best method (Mirchandani et al. 2014), but most pediatric cardiologists recommend indexing to height ( $\text{m}^{2.7}$ ) which appears to remove any relationship between LVM and age across adolescence (de Simone et al. 1995). Many pediatric HTN experts use an  $\text{LVM} \geq 38.6 \text{ g/m}^{2.7}$  (Daniels et al. 1995) as the cut-point to indicate increased LVM with  $\geq 51 \text{ g/m}^{2.7}$  as a clear indication that LVH is present and may require therapy (Expert Panel on Integrated Guidelines for Cardiovascular H, Risk Reduction in C, Adolescents and National Heart L and Blood I 2011). However, a single cut-point for this LVM index may not perform well in younger children so percentile grids have been developed (Khoury et al. 2009).

Left ventricular hypertrophy related to BP levels in adolescents was first demonstrated nearly 20 years ago. Daniels et al. (1998) found that 14% of children with HTN in a clinic setting had LVM  $>90\text{th}\%$  for age and 8% exceeded the adult cut-point of  $51 \text{ g/m}^{2.7}$ . Later studies demonstrated the risk for LVH increased with increasing levels of mean BP (Sorof et al. 2002; McNiece et al. 2007; Pieruzzi et al. 2015a, b) and BP variability (Sharma et al. 2013). Unfortunately, LVM is higher in youth with prehypertension (Urbina et al. 2011a; Pieruzzi et al. 2015a) as compared to normotensive subjects suggesting that TOD may occur at BP levels well below the current threshold for pharmacologic therapy. Odds for LVH in pediatric HTN patients are also higher in non-Caucasians even with similar BP levels (Hanevold et al. 2004; Pruetter et al. 2013).

Obesity also contributes to development of higher LVM (Urbina et al. 1995) which may complicate interpretation of the echo data since some normotensive obese youth have higher LVM than their lean counterparts (Falkner et al. 2013; Kharod et al. 2014). However, it appears that obese, hypertensive youth are the most likely to demonstrate elevated LVM (Falkner et al. 2013; Gidding et al. 2014).

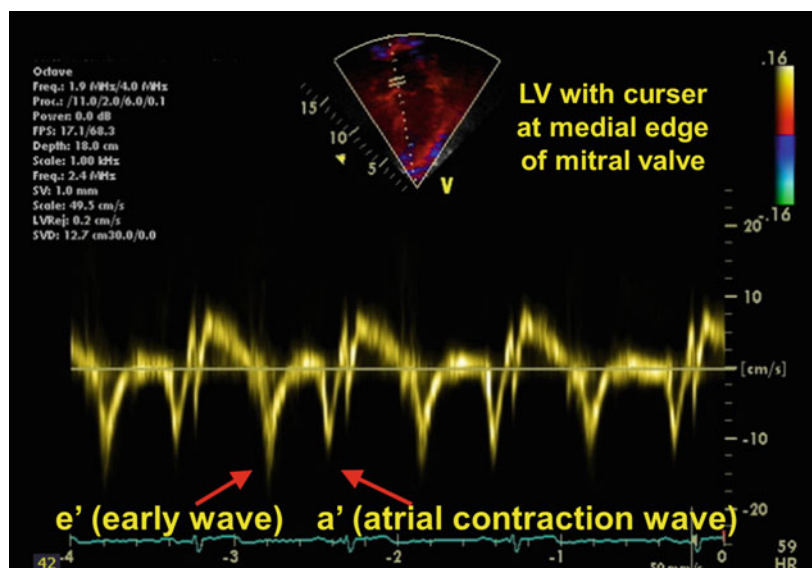
## Cardiac Function

Measures of cardiac function are also useful in the evaluation of the hypertensive child. The Doppler effect is the change in frequency of a wave for an observer relative to its source if the observer or source is moving. The most common example is the change in sound in a siren when an ambulance drives by. In echocardiography, the Doppler effect is used to determine the direction and speed of blood flow. Traditionally, diastolic function of the heart was measured by determining the velocity of the early wave “E wave” through the mitral valve as the heart relaxes and the valve opens for passive filling of the left ventricle. The atrial contraction wave or “A” wave is also measured and the E/A ratio is a crude measure of LV diastolic function (Feigenbaum 2010). Unfortunately, this

parameter changes with load (over or under hydration or low or high systemic BP) (Gomez et al. 2005). Therefore, less load-dependent measures are now used more frequently. Tissue Doppler Imaging (TDI) uses the Doppler effect to measure the movement of the myocardium throughout the cardiac cycle (Ho and Solomon 2006). This is usually performed at both the lateral and septal edges of the mitral valve from the apical four-chamber view. Although global (entire heart) values are usually reported, segmental results are also measured allowing for quantification of regional differences in cardiac function. Measurement of TDI does require specialized software on the echocardiography machine, but most modern devices are sold with this option. The parameters measured are the early wave (e’) and atrial wave (a’) (Fig. 4) (Ho and Solomon 2006). The E/e’ ratio is used as a reflection of LV filling pressures (Ho and Solomon 2006). Other TDI measures of diastolic function include e’/a’ and E/average of e’ and a’ (Feigenbaum 2010). Often, the lateral and septal measures are averaged.

Systolic function can be assessed by calculating the shortening fraction or % decrease in dimension of the LV during contraction. Tracings of the LV cavity during systole and diastole can also be used to calculate end-systolic and

**Fig. 4** Tissue Doppler imaging for measurement of early (e’) and atrial (a’) waves for calculation of diastolic function

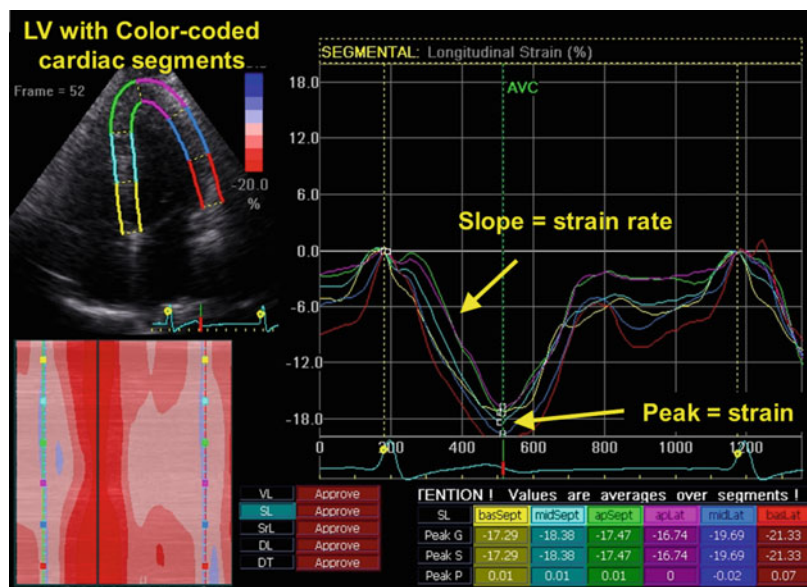


end-diastolic volume which can be used to measure ejection fraction or % of the volume of the heart ejected during systole (Feigenbaum 2010). A newer method to assess systolic function is cardiac strain. Strain (S) is a dimensionless parameter calculated from change in myocardial length that represents the % of deformation of the heart during a particular phase of the cardiac cycle. During contraction, myocardial cells decrease in length resulting in negative S, relaxation produces positive S. Strain Rate (SR) is rate of change of length representing speed of deformation (m/sec). This technique has high temporal resolution which allows depiction of regional asynchrony (Yip et al. 2003) which may be important in adults after myocardial infarction where only some segments of the heart have dysfunction. One method for measuring S obtains the velocities of myocardial tissue movement with TDI (Fig. 5). The advantage of this technique is that it requires no additional software on the ultrasound machine but does need a special program for offline analyses (proprietary or vendor-neutral software). The second method is called speckle tracking. Specialized ultrasound software identifies a speckle (acoustic backscatter generated by reflected US beam) in a designated search region. The speckles function as natural acoustic markers that can be tracked from frame to frame. The distance (S) and velocity

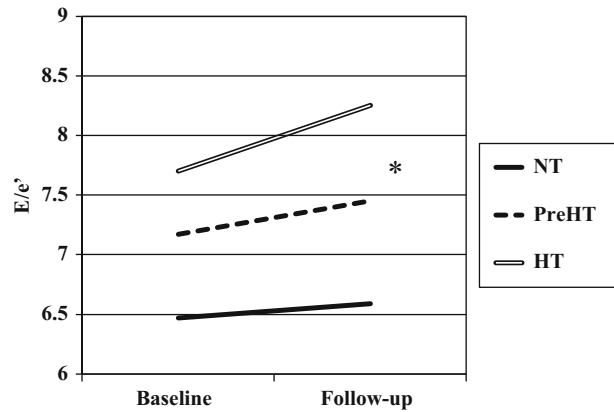
(SR) of movement of the speckles are obtained by automated measurement of distance between speckles. Advantage of speckle tracking as compared to TDI is that speckle tracking is angle independent thus not affected by misalignment between the cardiac axis and ultrasound beam. However, due to a lower frame rate the resolution is not as high as with TDI based strain measurements (Geyer et al. 2010).

The importance of these advanced measures of cardiac function is seen in studies showing their ability to predict hard CV events. A TDI  $e' < 3$  cm/sec predicted cardiac mortality even after correcting for clinical CV risk factors in adults (Wang et al. 2003). Global Longitudinal Strain  $> -12\%$  (more negative is better) added to the prediction of death even after correcting for CV risk factors even in subjects with normal EF (gross measure of systolic function) (Stanton et al. 2009). Little is known about these advanced measures of cardiac dysfunction in HTN. In one study of over 1000 adults, E/e' ratio declined across BP categories (stage II HTN, stage I HTN, preHT, NT) even if conventional E/A ratio was normal (Mogelvang et al. 2009). Diastolic dysfunction has also been seen in adults with HTN and type 2 diabetes mellitus (T2DM) who demonstrated nondipping pattern on 24 h ambulatory BP. Even though E/A ratio was normal, the nondippers had

**Fig. 5** Tissue Doppler imaging method for measurement of cardiac strain and strain rate. Each color-coded strain line represents one of six cardiac segments. Global longitudinal strain averaged  $-18.48$  (normal). Slope of the decline from 0 to  $-18$  represents strain rate



**Fig. 6** Diastolic function at baseline and after 5 years follow-up in 232 adolescents (mean age 17 years) and after 5 years of follow-up stratified by BP classification. \* $P \leq 0.05$  for normotensive (NT) < pre-hypertensive (PreHT) and hypertensive (HT) at both baseline and follow-up (Urbina unpublished data 2016)



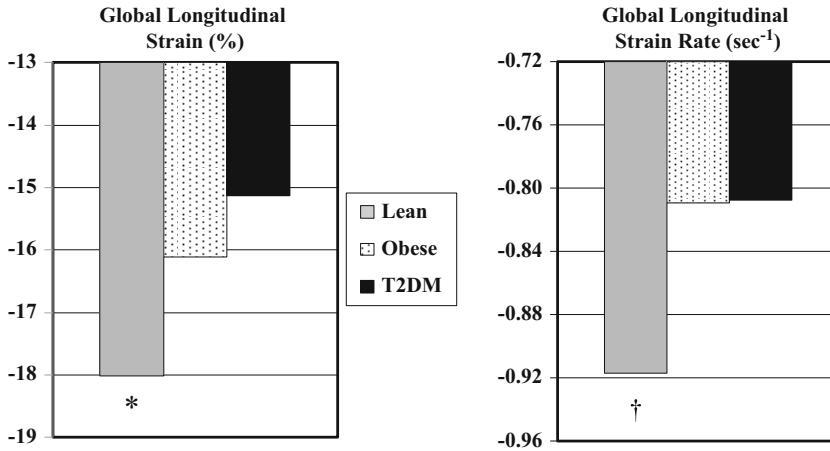
significantly increased  $E/e'$  ratio indicating diastolic dysfunction ( $P = 0.03$ ) and they had lower S and SR indicating subtle systolic dysfunction ( $P < 0.001$ ) (Kalaycioglu et al. 2014). Diastolic dysfunction has also been demonstrated in teens with HTN. Children with untreated HTN (mean age 13 years) had higher  $E/e'$  (more abnormal) compared to controls even though traditional  $E/A$  was normal (Agu et al. 2014). Recent data show that young adults with HTN not only start out with higher  $E/e'$  but they have more rapid deterioration in TDI measures over only 5 years of follow-up as compared to normotensive youth (Urbina, unpublished data 2017, (Fig. 6)) However, the importance of HTN as a risk factor for diastolic dysfunction in adolescents is not clear as some published reports show no association between BP levels and TDI measures (Gidding et al. 2014; Scavarda et al. 2014) whereas abnormal TDI has also been related to obesity (Pieruzzi et al. 2015b; Dusan et al. 2015).

When cardiac strain was evaluated in adults, subjects with both HTN and Type 2 DM had the lowest S and SR (Masugata et al. 2009). In another study of adults with no coronary artery disease and normal EF, of which 70% had HTN, decreased strain in all cardiac segments was seen with increasing degrees of LV hypertrophy (strain  $r = 0.453$ ; strain rate  $r = -0.430$ ) suggesting that BP-related heart thickening is associated with systolic dysfunction (Zoroufian et al. 2014). No studies of strain in hypertensive youth have been published but our preliminary data in subjects with mean age 22 years demonstrate a graded

decline in S and SR from normotensive to pre-hypertensive to hypertensive BP levels (Urbina, unpublished data 2017, (Fig. 7)).

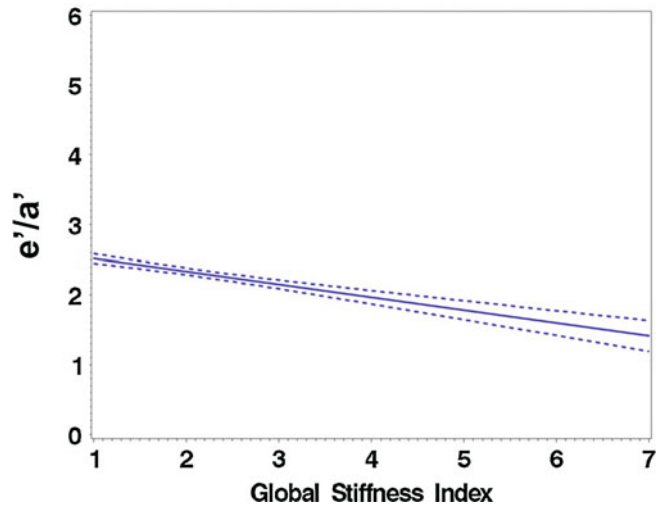
## Relationships between Vascular and Cardiac Dysfunction

People do not die of vascular dysfunction (“hardening of the arteries”), instead hard CV events occur due to damage to target organs caused by increased arterial stiffness and endothelial dysfunction, among other factors. Therefore, it is significant that pediatric studies have demonstrated evidence for a direct relationship between vascular stiffness and measures of TOD. Sorof et al. (2003), demonstrated that youth with thicker carotid arteries had greater LVM. This makes sense because a thicker vessel will increase the force which the heart pumps against (cardiac afterload). Similarly, global arterial stiffness calculated from carotid stiffness, AIx, brachial distensibility and PWV representing both peripheral and central arterial stiffness and wave reflections, was an independent determinant of LVM in adolescents even after adjusting for traditional CV risk factors (Urbina et al. 2011b). Similarly, increased global stiffness was associated with reduced diastolic function ( $E'/A'$  ratio) and lower S in this cohort (unpublished data). Similar to the relationship seen between increased arterial stiffness and LV mass, we have found a thicker carotid IMT is associated with reduced strain illustrating the important relationship between



**Fig. 7** Global longitudinal strain and strain rate in 309 young adults mean age 22 years stratified by BP category.  $P \leq 0.0001$  for: \*normotensive (NT) and prehypertensive (PreHT) < hypertensive (HT), †NT < PreHt and HT (Urbina unpublished data 2016)

**Fig. 8** Decline in diastolic function (tissue Doppler e'/a' ratio) at higher levels of arterial stiffness. \* $P \leq 0.001$  for slope differs from 0. Relationship remained significant after adjusting for CV risk factors with full model R (de Simone et al. 1995) = 0.29 (Urbina unpublished data 2016)



vascular and cardiac dysfunction (Urbina unpublished data 2017, (Fig. 8)). Therefore, the treatment of vascular function early in life is essential for prevention of adult CV events such as myocardial infarction and heart failure.

### Strategies for Improving Vascular and Cardiac Function

The Bogalusa Heart Study (Chen et al. 2005) and Young Finns study (Laitinen et al. 2012) were the first to demonstrate that “primordial prevention”

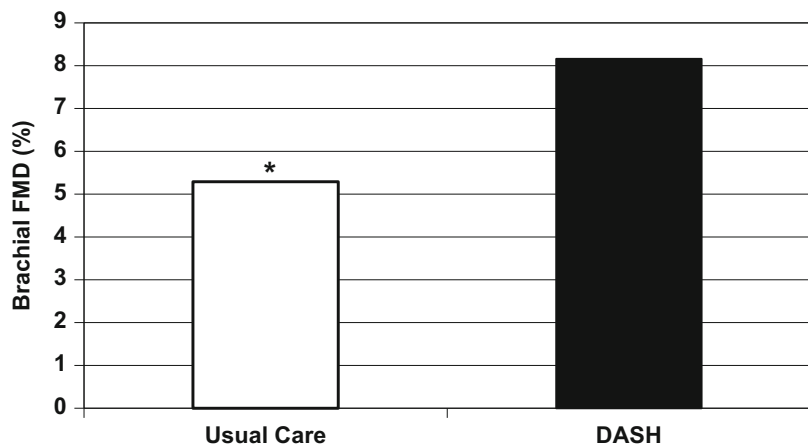
or the prevention of acquisition of CV risk factors from youth to adulthood was associated with lower cIMT as an adult. When data from both cohorts was combined, even if metabolic syndrome was present in childhood and was resolved by adulthood, age-related increase in cIMT slowed such that adult cIMT was the same as in subjects with consistently low-risk factor levels (Magnussen et al. 2012). Furthermore, ideal diet including high consumption of fruits and vegetables across the lifespan was associated with lower PWV (lower stiffness) as an adult in the Young Finns study (Aatola et al. 2010). The utility of

primordial prevention starting in youth is seen in analysis demonstrating that youth with T1DM who meet a greater number of ideal CV health metrics have lower PWV and AIx (Alman et al. 2014). Promotion of an active lifestyle is likely to improve arterial health as Edwards et al. demonstrated higher PWV in youth with lower levels of physical activity measured with accelerometry (Edwards et al. 2012). Primary prevention to treat existing CV risk factors is also effective. Pediatric studies have shown weight-loss induced drop in BP leads to regression of cIMT (Wunsch et al. 2006), and improvement in forearm blood flow (by venous plethysmography) (Ribeiro et al. 2005). Treatment of youth with familial hypercholesterolemia with statins induces regression of cIMT (Wiegman et al. 2004). Low-salt diet in teens with prehypertension and hypertension also led to normalization of BP and FMD after 6 months of intensive diet modification (Fig. 9). Unfortunately, a year after the end of the intervention, poor dietary patterns returned and FMD declined (unpublished data). Secondary prevention (aggressive treatment of high risk youth) (Expert Panel on Integrated Guidelines for Cardiovascular H, Risk Reduction in C, Adolescents and National Heart L and Blood I 2011) can also lead to improvement in both carotid thickness (Litwin et al. 2005) and stiffness (Tawadrous et al. 2012) in youth after kidney transplant. Similarly, the treatment of obstructive sleep apnea after adenotonsillectomy results in lower BP and improved LFD response (Gozal et al. 2007) To date, there have been no randomized clinical trials

to evaluate response of vascular parameters to initiation of antihypertensive drugs. However, an intent-to-treat study showed 62% of subjects (median age 15 years) had reduction in cIMT after 1 year of antihypertension treatment (Niemirska et al. 2013).

Fortunately, improvement in cardiac parameters is possible with good BP control. Treatment of BP with ACE inhibitors has been proven to lead to reduction in LVM in both adults (Lonn et al. 2004) and children (Niemirska et al. 2013; Seeman et al. 2007) In one pediatric study, a modest drop of 7–11 mmHg in BP resulted in a reduction in prevalence (Seeman et al. 2007) of LVH from 42 to 11% after 6 months of treatment. A somewhat smaller reduction in prevalence of LVH was seen with strict BP control in the ESCAPE trial (Effect of Strict BP Control and ACE Inhibition on Progression of Chronic Renal Failure in Pediatric Patients) (Kupferman et al. 2014). Furthermore, the intensive treatment group had a significant increase in midwall fractional shortening (12% vs 8% in conventional treatment,  $p = 0.05$ ) (Matteucci et al. 2013). Although research in adults show treatment of HTN results in improvement in diastolic function (Bello et al. 2004) and strain (Manov et al. 2012) no similar pediatric studies been conducted. However, BP lowering induced by weight-loss after bariatric surgery was associated with improvement in TDI measures (Ippisch et al. 2008) and aerobic exercise improved BP and cardiac strain in obese adolescents (Ingul et al. 2010).

**Fig. 9** Improved FMD in Youth with HTN after 6 months of DASH-4-Teens Diet  $p = 0.05$ .  $N = 64$ , mean age 15 years (Reproduced with permission, Urbina 2016)



## Summary

Hypertension is a major risk factor for hard CV events (Nilsson 2012). Increasing evidence demonstrates that elevated BP increases risk through its adverse effects on arterial remodeling resulting in increased vascular thickness and stiffness and decreased endothelial function. This arterial dysfunction in turn leads to adverse alterations in cardiac structure and function. Luckily, lifestyle modifications show promise in improving arterial and cardiac parameters but much work remains to be done. Gaps in knowledge include: (a) lack of sufficient normative data on CV parameters across age, sex, and race/ethnicity; (b) insufficient data describing effect size comparing the healthy CV system to subjects with a variety of pediatric conditions; (c) lack of large, robust, randomized clinical trials to demonstrate improvement in arterial and cardiac measures in youth; and (d) lack of standard approaches for assessing CV dysfunction thus limiting comparison among studies. With continued research we may someday develop effective and safe therapies for pediatric HTN patients and thus reduce the burden of CV diseases around the world.

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# The Role of ABPM in Evaluation of Hypertensive Target-Organ Damage

Empar Lurbe and Josep Redon

## Abstract

Despite evidence of an increasing prevalence of hypertension in the young, the consequences of early onset hypertension are not well established and often overlooked. Consequently, screening for early organ damage such as left ventricular hypertrophy, albuminuria, increased carotid intima-media thickness, pulse wave velocity, and even subtle clues to impaired brain function is key to evaluation. Over the last years ambulatory blood pressure monitoring has been introduced to evaluate blood pressure in the pediatric population, contributing substantially to knowledge about clinically relevant issues. Present guidelines recommend currently known conditions for which ambulatory blood pressure monitoring is useful and for which it will provide additional information in children and

adolescents. The relation between ambulatory blood pressure and hypertension-induced organ damage is a key issue for ambulatory blood pressure monitoring. In children, the accurate identification of hypertension at the earliest possible age should logically give health-care providers the opportunity to initiate preventive measures, thereby potentially reducing the chance of developing end-organ damage and its attendant morbidity and mortality.

## Keywords

Hypertension • Children and adolescents • Ambulatory blood pressure • White-coat hypertension • Masked hypertension • Target organ damage

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## Introduction

Office blood pressure (BP) is routinely measured because epidemiological data established an association between elevated office BP and cardiovascular (CV) morbidity and mortality in various populations. However, BP varies substantially over each 24-h period (Mancia et al. 2000). Thus, in-office BP may not reflect a patient's true BP, and the value of isolated in-office BPs to assess individual cardiovascular (CV) risk is poor.

The introduction of ambulatory blood pressure monitoring (ABPM) with the use of automatic devices that record BP during regular activities of daily life has provided information that facilitates a better understanding of BP behavior and its role in the pathophysiology of hypertension-induced organ damage. From the beginning of the technology that permits ABPM assessment, its potential value over office BP measurements was tested by assessing the relation between BP values and the presence (or absence) of target organ damage (TOD), based on the hypothesis that organ damage mainly depends on the BP level and the amount of time that it is elevated. In fact, in a seminal paper of Sokolow et al. (1996), out-of-office BP measured with a semiautomatic portable recorder showed a better relation to the severity of TOD than office BP.

After that initial pioneering observation (Sokolow et al. 1996), many studies analyzed how the BP parameters obtained by using ABPM are related to the presence or the development of hypertension-induced TOD, as well as how antihypertensive treatment and BP reduction may ameliorate TOD. Such information is relevant in adult population, but it is even more important in children and adolescents, who generally have not yet developed cardiovascular or renal events at the time of assessment. A review of the available information about the role of ABPM in assessing TOD in children and adolescents, including cross-sectional and follow-up studies, is presented in this chapter.

## Hypertension-Induced Organ Damage

Hypertension-induced morbidity and mortality is produced through the impact of elevated BP on the heart, blood vessels, kidney, and central nervous system. Evaluation of early TOD is an important step in a cost-effective risk stratification strategy in order to reduce cardiovascular and renal damage. Despite the difficulties in quantifying how risk increases with the presence of TOD damage in one or more organs, obtaining quantitative data renders prediction more accurate for the given BP value. There is consensus that the presence of TOD in multiple organs implies increased cardiovascular risk. The majority of children and adolescents have inherently low or moderate risk, but assessment for TOD may lead to upgrading the risk if TOD is found.

The European Society of Hypertension (ESH) Guidelines in children and adolescents, published in 2016 (Lurbe et al. 2016), state, “*Once HTN is confirmed, organ damage evaluation should be assessed due to the importance of subclinical organ damage as an intermediate stage in the continuum of vascular disease. Subsequently, evaluation of organ damage is also useful as an intermediate endpoint for monitoring treatment.*” Determination of left ventricular mass, urinary albumin excretion, glomerular filtration rate, carotid wall thickness, and pulse wave velocity, the most commonly used markers of TOD, is important – based on availability, cost, and clinical significance. Criteria recommended by the ESH to define hypertension-induced TOD are shown in Table 1. The importance of repeated TOD assessment during the follow-up of patients has been emphasized. The ESH Guidelines 2016 (Lurbe et al. 2016) recommended “. . . *In patients with LVH or inadequately controlled BP, cardiac assessment should be repeated at least every six months. . . Patients with well-controlled HTN and no target organ pathology should be monitored at larger intervals, e.g. every 12 to 24 months, to rule out de novo TOD. . .*”. The 2017 American Academy of Pediatrics childhood hypertension guideline (Flynn et al. 2017) contains slightly different recommendations which are summarized in the Appendix of this text.

In adults, utilizing electrocardiography or echocardiography to assess changes in left ventricular

**Table 1** Criteria to define hypertension-induced target organ damage according to ESH Guidelines

<i>Left ventricular hypertrophy</i>	Left ventricular hypertrophy should be defined as LVMI or relative wall thickness (RWT) $\geq$ 95th percentile by age and gender
<i>Kidney</i>	Albuminuria (as measured by urinary albumin/creatinine quotient $>30$ mg/g creatinine or $>3$ mg/mmol creatinine) or even proteinuria (as measured by urinary albumin/creatinine quotient $>300$ mg/g creatinine or $>30$ mg/mmol creatinine) or by 24 h urinary protein excretion ( $>200$ mg/m <sup>2</sup> /day)
<i>Carotid intima thickness</i>	cIMT $\geq$ 95th percentile by age and gender
<i>Pulse wave velocity</i>	PWV $\geq$ 95th percentile by age and gender

LVMI left ventricular mass index, RWT relative wall thickness, cIMT carotid intima media thickness, PWV Pulse wave velocity

Source: Lurbe et al. (2016)

hypertrophy (LVH) induced by treatment reflects the effects of BP control on cardiovascular events, thereby offering valuable information on whether patients are more or less effectively protected by the specific treatment strategy being used. In fact, several studies have demonstrated a reduction in the risk of mortality or in the incidence of stroke, coronary events, and congestive heart failure among hypertensive patients who achieve a reduction in electrocardiography voltage, strain, or echo left ventricular mass with therapy (Devereux et al. 2004; Gerds et al. 2012; Mancia et al. 2013). Despite some initially inconsistent results, solid evidence now suggests that treatment-induced changes in urinary protein excretion reflect changes in risk. Indeed, a reduction in total mortality and cardiovascular mortality has been reported when a significant reduction in urinary albumin excretion is achieved (Ibsen et al. 2004; Schmieder et al. 2011). However, it is not yet clear whether treatment-induced changes in vascular reactivity, carotid intima media thickness (ITM), and pulse wave velocity (PWV) signify reduction in risk, since the changes over time are minimal and studies that address this question are limited.

Despite the many studies demonstrating an association between regression of TOD during

antihypertensive treatment and decreased mortality and cardiovascular and renal morbidity, some key questions about how best to use the assessment of TOD clinically remain. For example, which marker or markers should be used, what is the most appropriate timing to repeat TOD assessment and whether or not changes in one organ can be assumed to reflect what is occurring in the other organs is unclear. Ultimately, whether some markers of TOD should be targeted and assessed after antihypertensive therapy has reduced BP toward or to goal is unknown.

## Ambulatory Blood Pressure Monitoring

Over the last several years ABPM has been introduced in the field of pediatric hypertension, and it has become a useful tool for making clinical decisions. Out-of-office BP measurements, during routine activities of daily life, can be obtained using 24-h ABPM. Ambulatory BP measurement may now be considered an indispensable tool in the diagnosis and management of HTN. Detection of subtle BP abnormalities, early identification of HTN, and 24-h control of HTN are all facilitated by ambulatory BP measurement. Given the enormous relevance of BP control in childhood HTN for long-term cardiovascular health, ABPM should be the preferred technology for the management of HTN in children. ESH guidelines for performance of ABPM (Lurbe et al. 2016) are shown in Table 2. A summary of ABPM-related recommendations from the 2017 American guidelines (Flynn et al. 2017) can be found in the Appendix of this text.

The averages of daytime, nighttime, 24-h ambulatory BP, and other parameters, especially relating to BP variability, such as circadian and intrinsic variability can also be obtained (Parati 2005) with ABPM. Moreover, ABPM can help to identify periods of uncontrolled BP or excessive BP reduction (Pickering 1992). Although office BP is still the reference for the diagnosis of hypertension (HTN), ambulatory BP is helpful in defining BP categories. Therefore, the availability of reference values of “normalcy” is a key issue. Ambulatory systolic and diastolic BP values have been obtained

**Table 2** Recommendation for ABPM according to ESH guidelines

During the process of diagnosis	Confirm hypertension before starting antihypertensive drug treatment in order to avoid treatment of white-coat hypertension Type 1 and type 2 diabetes Target organ damage (LVH, microalbuminuria) and office BP normal (masked hypertension) Chronic kidney disease Severe obesity with or without sleep-disordered breathing Discrepancy between office BP and home BP Hypertensive response during the treadmill test Renal, liver, or heart transplant
During antihypertensive drug treatment	Evaluate for apparent drug-resistant hypertension Symptoms of hypotension Assessment of BP control in children with target organ damage
Clinical trials	
Other clinical conditions	Suspicion of catecholamine-secreting tumors Autonomic dysfunction

*LVH* Left ventricular hypertrophy

Source: Lurbe et al. (2016)

from some European populations (Wühl et al. 2002) and are available for sex, age, or height.

Using both office and ambulatory BP, four possible conditions arise. When both office and ambulatory BP (two different ways of measuring BP) are in agreement, normotension or HTN is confirmed, depending on the level of the BP. When the values are discrepant, normotensive with one method, and hypertensive with the other, the patient has either white-coat HTN or masked HTN. White-coat HTN (WCH) is the elevation of a patient's BP in response to the observer measuring the BP and the office milieu (Sorof et al. 2001; Matsuoka et al. 2002; Stabouli et al. 2005), but normal BP otherwise. In children, WCH has been defined as a normal daytime ambulatory BP but an elevated in-office BP. The opposite phenomenon, masked HTN, consists of elevated daytime ambulatory BP with normal office BP (Lurbe et al. 2005). The discrepancy between in-office

and ambulatory BP is clinically relevant and is one of the fundamental arguments for the use of ABPM. The prevalence and clinical significance of these two discrepant conditions, white-coat and masked HTN, are not well defined, since they differ depending on the patient.

## White-Coat Hypertension

The prevalence of white-coat HTN differs greatly among published studies, with values ranging from very low to as high as 44% (Lurbe et al. 2013b). Such variation is due to the threshold selected to define HTN for ambulatory BP (ABP) values, and also on the population included and the procedure used for the in-office BP measurements to which the ABP values are compared. Children with confirmed WCH tend to have a higher left ventricular mass index (LVMI) as compared to children who are confirmed to be normotensive, although no significant differences in LVMI have been observed between the groups (Kavey et al. 2007; Stergiou et al. 2008; Lurbe et al. 2013). To date, no long-term follow-up data of children with white-coat HTN at initial assessment is available; thus the reproducibility of the phenomenon is unclear, and assessment of the impact of this condition is unknown. Hence, it remains to be clarified whether WCH is an innocuous phenomenon or a prelude to future sustained adult HTN.

## Masked Hypertension

The opposite phenomenon is termed "masked HTN," BP that is normal in the office but elevated elsewhere. In studies that have explored this condition, masked HTN occurred in approximately 10% of children and adolescents (Matsuoka and Awazu 2004; Stabouli et al. 2005; Lurbe et al. 2005; Stergiou et al. 2008; Di Salvo et al. 2011), although one study observed a higher prevalence of 38% (Mitsnefes et al. 2010). The persistence and clinical importance of the phenomenon was analyzed in a prospective study involving 234 adolescents (Lurbe et al. 2005), in 40% of whom the abnormal elevation of the daytime ambulatory BP persisted. Adolescents with



persistent masked HTN were more than twice as likely to have a parental history of HTN. Those with masked HTN also had a higher ambulatory pulse rate, a higher body mass index (BMI), and a more frequently LVH than normotensive participants. Alone, or in combination, these characteristics appear to predispose people to develop HTN and increased cardiovascular risk in later life. The long-term prognostic value of masked HTN to progress to HTN in youth has established that masked HTN is a precursor of sustained HTN. The risk of developing sustained HTN after the diagnosis of masked hypertension is reported as higher in boys than in girls (Lurbe et al. 2013a).

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## Ambulatory Blood Pressure Monitoring and Target Organ Damage

### Left Ventricular Mass

The abnormal increase of LVM and/or geometry has been recognized as one of the most important markers of risk for hypertension-induced cardiovascular morbidity and mortality in adults. In children and adolescents, the relation between HTN and LVM is more difficult to recognize, because children and adolescents grow rapidly and their BP increases with age. Cross-sectional studies have shown that the major determinants of left ventricular growth are body size and sex, with a smaller contribution from BP (Malcolm et al. 1993; de Simone et al. 1995). The important contribution of somatic growth and the recognition that lean body mass contributes more to cardiac growth than fat mass were nicely demonstrated in the Bogalusa Heart Study (Urbina et al. 1995). In a longitudinal study, the Medical College of Virginia Twin Study, LVM tracks from early to late adolescence to about the same degree as other important risk factors, such as BP and cholesterol (Schieken et al. 1998). The potential role of adiposity in the increment of LVM has been highlighted (Sivanandam et al. 2006). Adiposity and LVM are related in childhood, and this association tracks and becomes stronger in young adulthood. Moreover, the increase in LVM from child to young adult is related to the degree of increase in BMI.

Although epidemiological studies do not help to establish the difference between appropriate and excessive increases in left ventricular mass, operational thresholds have been established. Thresholds of both the allometric definition of excessive mass ( $>51 \text{ g/m}^2$ ) and the percentile distribution of mass and geometry have been recommended. Using these operational thresholds, several have analyzed the prevalence of LVH in normotensive and hypertensive children and adolescents. In those children that are hypertensive, the prevalence of LVH ranges from 24% to 40% in different pediatric studies (Daniels et al. 1998; Sorof et al. 2002; Flynn and Alderman 2005; Litwin et al. 2006; Richey et al. 2008; Maggio et al. 2008).

Several studies in the pediatric age group have found that systolic BP and LVMI are positively associated across a wide range of BP values, with no clear threshold to predict pathologically increased LVMI. Sensitivity and response to hemodynamic load seems to vary with age, sex, and ethnicity, which explains some of the differences among published results. The relation between LVMI and systolic BP is more evident when BP is measured using 24-h ambulatory BP monitoring in patients from different sources and underlying conditions (Table 3). The information provided from these studies, however, is heterogeneous. The results of these studies reflect the parameters recorded and analyzed related to the presence or absence of LVH or related to participants with largely differing LVM. The parameters most closely associated with LVM are the averages of 24 h, daytime, or nighttime. Some other studies found a positive association with the circadian variability. A few studies did not find a significant relation between measured BP parameters and LVM when BMI was included in the regression models (Dušan et al. 2015). Moreover, when office BP was measured successively over time, ambulatory BP was not superior to office BP (Bjelakovic et al. 2015). In adults intrinsic variability in 24-h BP had been associated in predicting the development of TOD independent of absolute BP values (Kikuya et al. 2000; Parati 2005; Mancia et al. 2007). Nevertheless, in children and adolescents no validated information exists.

**Table 3** Studies assessing the relation between ambulatory BP and left ventricular mass in different study populations

Author	Population characteristics (number and description)	Prevalence white-coat HTN	Prevalence masked HTN	Association with LVH	ABP > OBP	ABP parameter-related
Belhssa et al. (1998)	69 referred subjects	–	–	–	Yes	Nocturnal SBP with LVMI
Calzolari et al. (1998)	30 renal transplant	–	–	–	Yes	24-h, daytime, and nighttime SBP and DBP with LVMI
Hauser et al. (2000)	95 aortic coarctation	–	–	–	Yes	24-h SBP with LVH
Rucki (2000)	108 referred subjects	–	–	–	Yes	Daytime SBP with LVMI
Lurbe et al. (2005)	592 population study	1.7%	7.6%	LVH in masked	Yes	24-h with daytime SBP
Stabouli et al. (2005)	85 referred subjects	12.9%	9.4%	LVH in masked	Yes	–
McNiece et al. (2007)	163 referred subjects	Stage 1–34% <sup>a</sup> Stage 2–15% <sup>a</sup>	20%	LVH in masked	Yes	–
Kavey et al. (2007)	119 referred subjects	52%	–	LVH in white-coat	Yes	–
Lande et al. (2008)	217 referred subjects	31%	–	LVH more than normotensives	–	–
Stergiou et al. (2008)	102 referred subjects	18%	11%	–	–	–
Lande (2008)	81 subjects matched	–	–	LVH in sustained HTN	Yes	–
Stabouli et al. (2009)	124 referred subjects	–	–	LVH hypertensive and prehypertensive	Yes	–
Richey et al. (2010)	68 referred subjects	–	–	–	Yes	Nocturnal SBP with RWT 24-h more eccentric LVH
Mistnefes et al. (2010)	189 CKD stage 2–4	–	–	–	Yes	–
Stergiou et al. (2010)	82 referred subjects	–	–	–	Yes	24-h PP LVMI
Sinha et al. (2011)	49 CKD normotensive	–	–	–	No	Multiple Office-BP overtime better
Basiratnia et al. (2011)	66 post-transplant	–	–	–	Yes	All ABPM averages
Bostanci et al. (2012)	50 metabolic syndrome	–	–	–	Yes	SBP load
Sharma et al. (2013)	72 referred subjects	–	–	–	Yes	Nighttime SBP with daytime SBP

(continued)

**Table 3** (continued)

Author	Population characteristics (number and description)	Prevalence white-coat HTN	Prevalence masked HTN	Association with LVH	ABP > OBP	ABP parameter-related
Bjelakovic et al. (2013)	67 referred subjects	–	–	–	Yes	No specific parameter when BMI is included
Dušan (2015)	103 obese subjects	–	–	–	No	Peak SBP
Bjelakovic et al. (2015)	94 referred subjects	–	–	–	No	No parameters related to LVMI

*LVMI* left ventricular mass index, *LVH* left ventricular hypertrophy, *RWT* relative wall thickness, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *CKD* chronic kidney disease, *HTN* hypertension, *MHTN* masked hypertension, *OBP* office BP, *ABP* ambulatory BP, *ABP > OBP* ambulatory BP superior than office BP

<sup>a</sup>Stage 1 and stage 2 were defined according to the ESH Guidelines (Lurbe et al. 2016)

A few studies have analyzed changes in LVM or geometry during antihypertensive treatment and the association with the level of BP control. Eighty-four patients with chronic kidney disease (CKD) from the Effect of Strict Blood Pressure Control and Angiotensin Converting Enzyme (ACE) Inhibition on Progression of Chronic Renal Failure in Pediatric Patients (ESCAPE) trial were randomized to conventional or intensified BP control by using 24-h ABPM. After 1 year of treatment, LVH decreased from 38% to 25%, and LVM was reduced but only in those with LVH at baseline. Although reduction in LVM was not related to BP values, it was related with functional improvement assessed by mid-wall fractional shortening, observed mainly in those with intensified BP control. This improvement was related to BP reduction independent of other parameters including LVMI (Litwin et al. 2010; Matteucci et al. 2013) assessed the changes in office BP, ABP, BMI, waist and hip ratio, and LVM during 1 year of antihypertensive treatment. The reduction in LVM was related to changes in waist and hip ratio but not to changes in office BP or ABP.

### Glomerular Filtration Rate and Urinary Albumin Excretion

Renal disease in children is frequently associated with elevated BP. An increase in BP as a consequence of kidney disease contributes to the

progression of renal damage. Rapid progression of kidney disease in concert with poorly controlled hypertension may result in end-stage renal insufficiency during childhood. In parallel, cardiovascular damage develops, although the cardiovascular consequences of childhood onset HTN, such as LVH and dysfunction and atherosclerosis, may not become clinically relevant before adulthood. With the decline in the number of functional nephrons, a further increase in BP occurs, creating a vicious cycle that not infrequently progresses to end-stage renal disease (ESRD). Furthermore, progressive vascular disease compromises renal blood supply and contributes still further to the vicious cycle by increasing renal damage.

Evidence of the importance of ABP values in assessment of and intervention in the progression of renal disease has come from several clinical studies in children with or without established renal insufficiency. Besides the glomerular filtration rate (GFR) reduction, an increase in urinary albumin excretion (UAE) is a marker of HTN-induced renal damage although in part reflects increment of endothelial permeability. Proteinuria, a marker of glomerular damage in primary and secondary glomerulopathies, can increase as a consequence of elevated BP values, so it should be targeted by lowering BP. Even small amounts of UAE, microalbuminuria, are correlated with the progression of nephropathy and to a higher cardiovascular risk. Initially,

information came from cross-sectional studies which demonstrated a clustering of cardiovascular risk factors and TOD associated with a subtle increase in UAE. The role of microalbuminuria assessment in pediatrics was initially limited to diabetes, however, it is now recommended by the ESH that microalbuminuria should be considered in the assessment of hypertensive children and adolescents (Lurbe et al. 2016). The 2017 American guideline, on the other hand, came to the opposite conclusion and does not recommend assessment of microalbuminuria (Flynn et al. 2017).

The regular use of ABP monitoring in patients with renal disease not only permits a better assessment of BP values but also frequently uncovers circadian variability abnormalities. Normally, BP decreases at night, or “dips.” A blunted nocturnal BP fall, a “non-dipper” pattern, is characteristic for renal disease, whatever the etiology. The role of the diurnal BP pattern as either a marker of or a pathogenic factor for kidney damage has been stressed in many studies. Patients with a decrease in GFR are likely to show less of a nocturnal dip in BP and frequently display an increase in nighttime versus daytime BP levels when these are compared with the BP profiles from normotensive or hypertensives with a normal GFR (Portaluppi et al. 1991; Luik et al. 1994; Lurbe and Redon 1999).

The prevalence of non-dipping rises with worsening renal function and when GFR decreases to extremely low levels of <10 ml/min. More than 70% of patients with ESRD show the non-dipper pattern. After renal transplantation, an abnormal BP decline during nighttime occurs almost universally in adults as well as in children due to multiple factors including the impact of glucocorticoid and immunosuppressive therapy (Faria Mdo et al. 1995; Lingens et al. 1996; Farmer et al. 1997; Calzolari et al. 1998; Morgan et al. 2001; Mistnefes and Portman 2003). Some of these patients may experience reverse dipping, with nighttime BP exceeding daytime BP. In a study by Sorof et al. (2000), 72% of such patients have an attenuated decline in nocturnal systolic BP, with 24% having greater nighttime than daytime BP. Even in the absence of renal insufficiency, the prevalence of the non-dipper pattern is high in such diseases as autosomal dominant polycystic kidney disease (Li Kam Wa

et al. 1997), reflux nephropathy (Lama et al. 2003; Patzer et al. 2003), unilateral renal agenesis (Seeman et al. 2006), and type 1 diabetes (Lurbe et al. 1993, 2001, 2002). It has also been reported high in essential HTN (Seeman et al. 2012).

The greatest amount of information concerning reversed circadian rhythm has been obtained in patients with diabetes mellitus. Studies of spectrum of abnormalities of circadian BP variability in type 1 diabetes in all stages of diabetic nephropathy show that about 58% of the microalbuminuric and 80% of the frankly macroalbuminuric patients evaluated have a persistently blunted BP fall during the night (Lurbe et al. 2001). The reduction in the BP nocturnal fall is independent of the disease duration (Lurbe et al. 2001). In type 1 diabetes, the presence of persistent microalbuminuria parallels an early BP deregulation observed during sleep, even in the absence of HTN. When overt nephropathy becomes established, HTN is present and abnormalities in the circadian BP profile are more conspicuous. Moreover, in a study of adolescents with type 2 diabetes 40% of 26 patients had elevated systolic BP while awake, which was associated with elevated urinary albumin excretion (Ettinger et al. 2005). A pathogenic role of nocturnal systolic BP has been associated with the development of microalbuminuria in normotensive patients with type 1 diabetes (Lurbe et al. 2002; Gallego et al. 2005; Dost et al. 2008). An increase in BP during sleep preceded the development of microalbuminuria, whereas in those whose BP decreased normally during sleep the progression to microalbuminuria was less frequent (Lurbe et al. 2002).

Mechanisms underlying circadian variation abnormalities are not well understood. The potential role of sympathetic overdrive was ruled out in one small study comparing plasma norepinephrine values in dipper and non-dipper end-stage renal disease patients (Van de Borne et al. 1993). Some authors write that the presence of the non-dipper pattern in patients with end-stage renal disease depends on the presence of autonomic neuropathy or glucocorticoid treatment, rather than on end-stage renal disease per se (Redon and Lurbe 2002), although when GFR decreases, the prevalence of a non-dipper pattern increases.

Whether or not an abnormal circadian variability can contribute to further kidney damage is a matter of debate. Some evidence supports of the concept that transmission of aberrant systemic BP may constitute a mechanism that induces renal damage, whereas other evidence supports the concept that the non-dipping pattern is a consequence of the renal damage itself. In some cases, higher BP values during nighttime may contribute to the progression toward renal insufficiency, while in other cases the values are a consequence of the altered renal function itself. In the latter, higher BP may also participate in accelerating the loss of renal function, contributing, in turn, to more severe hypertension.

There is practical utility associated with the assessment of circadian variability. First the pattern of circadian rhythm in BP can be used in the prognosis of disease. Second, it can aid in the identification of patients with suboptimal BP control. The presence of nocturnal hypertension may contribute not only to a faster decline in renal function over time but also to the development of more severe hypertensive cardiovascular disease. Assessing nocturnal BP as a target for protecting against kidney damage seems to be important in the treatment of renal disease, although the optimal nocturnal BP goal needs to be defined in prospective studies. Until now BP values which are persistently above the 95th percentile for age, sex, and height have determined the need to initiate antihypertensive treatment (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004; Lurbe et al. 2016; Flynn et al. 2017). Nevertheless, the presence of a non-dipping pattern, when BP values are below the 95th percentile, has not been deemed sufficient cause to start treatment. Future studies need to be conducted to address this specific point.

Only a few studies have analyzed the relation between changes in ABPM and renal outcomes, using both UAE and ESRD, in children and adolescents. Our group performed follow-up studies that demonstrated that in normotensive normoalbuminuric patients with type 1 diabetes, persistently blunted BP circadian variability was associated with an increased risk of developing

microalbuminuria and early diabetic nephropathy (Lurbe et al. 2002). A more recent study with 6 years follow-up of normotensive normoalbuminuric patients with type 1 diabetes demonstrated that daytime systolic BP at baseline was a risk factor for the development of microalbuminuria (Perrin et al. 2010). For children with CKD, the prospective randomized ESCAPE trial has provided evidence that strict BP control aiming for a 24-h BP target below the 50th percentile leads to improved long-term renal survival (ESCAPE Trial Group 2009). The study demonstrated that superior long-term nephroprotection is achieved by targeting for a low-normal 24-h mean arterial pressure as compared to a high-normal BP target (ESCAPE Trial Group 2009). Furthermore, the use of ambulatory BP monitoring in the pediatric ESCAPE trial may have allowed more accurate monitoring of BP values than achieved when only casual BP readings were obtained.

## **Structural and Functional Vascular Alterations**

### **Carotid Intima-Media Thickness**

Hypertension-induced abnormalities in arterial structure and function are important because they appear to be related to the development of morbidity over time. Assessment of vascular damage, however, received little attention prior to the advent of the advanced ultrasound technology that permits noninvasive study of vascular walls and lumens. Intima-media thickness (IMT) measurement at the carotid artery is the most common method used to assess structural abnormalities. Since age and sex influence the values of IMT (Jourdan et al. 2005), measured values should be related to percentiles or expressed as standard deviation scores.

In the few pediatric studies available, hypertensive children and adolescents tend to have an increase in IMT as compared to normotensive controls (Sass et al. 1998; Sorof et al. 2003; Litwin et al. 2006). The impact of other cardiovascular risk factors besides HTN, such as cholesterol levels, smoking, metabolic syndrome, or inflammatory disease, needs to be considered in the interpretation of IMT results, since these

variables have been associated with IMT results as well. Moreover, measurement is not trivial and subject to some observer bias. Hence, despite the increasing evidence for its predictive value in cardiovascular disease, IMT assessments have not yet been recommended universally for routine clinical use in children and adolescents.

At present the information about the relation between carotid wall-thickness and ABP has come from a small number of studies in obese and nonobese children. The results of both carotid wall thickness and ABP are contradictory; in some studies (Stabouli et al. 2005, 2012) no relation between carotid wall thickness and ABP was observed, while in others, strong evidence was provided that carotid IMT is increased in childhood primary HTN, related to 24-h ABP (Davis et al. 2001; Lande et al. 2006; Litwin et al. 2006) and independent of the effect of obesity (Stabouli et al. 2012). In type 1 diabetes nocturnal BP elevation (Lee et al. 2011; Atabek et al. 2014) or metabolic syndrome (Civilibal et al. 2014) was associated with the presence of increased IMT. Recently, an association between intrinsic BP variability and greater IMT, independent of 24-h ABPM, has been reported (Ntineri et al. 2015). In a follow-up study of children with primary HTN the effects of 12 months of antihypertensive therapy on 24-h ABP and TOD were assessed. A significant reduction of carotid IMT was observed in those patients whose ABP load was reduced with therapy (Litwin et al. 2006).

### **Pulse Wave Velocity**

Carotid-femoral pulse wave velocity has been considered the best noninvasive method of choice for assessing arterial stiffness in the great vessels. An increased carotid-femoral pulse wave velocity is considered a marker of early organ damage (Mancia et al. 2013). In ESRD patients it is considered a prognostic marker of mortality. Recently, reference data have been published for children and adolescents, which provide a standard against which to evaluate early alterations of large vessel in high-normal and hypertensive patients' young people (Elmenhorst et al. 2015).

The relation between carotid-femoral pulse wave velocity and of ABPM values to physiological measures has been analyzed in few studies that included patients with obesity and diabetes. ABPM was correlated between 24-h pulse pressure (Stergiou et al. 2010), 24-h and daytime variability (Stabouli et al. 2015) as well as a loss of dipping (Correia-Costa et al. 2016). In addition, insulin resistance has been related to elevate BP in obese children and appears to be related to by arterial stiffness. Obese children had a higher nighttime BP when compared to a control group of normal weight, independently of insulin resistance and arterial stiffness. No relation was found between insulin resistance and arterial stiffness and nocturnal systolic BP (Hvidt et al. 2014).

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## **Central Nervous System**

Traditional diagnostic procedures to assess early central nervous system TOD included neurologic and ophthalmologic clinical evaluation, electroencephalography, and, in emergency cases, cranial magnetic resonance image in order to exclude intracranial hemorrhage or cerebral edema. Magnetic resonance imaging has largely replaced the computerized tomography scan, due to its better detection of small, silent brain infarcts, micro bleeds, and white matter lesions. As the prevalence of pediatric HTN is increasing, there has been increased interest in evaluating its impact on neurocognitive function. There is now emerging evidence that children with HTN manifest neurocognitive differences when compared with normotensive controls, potentially representing early signs of hypertensive TOD to the brain.

Neurocognitive studies of children have focused principally on cognitive domains of attention and working memory, executive functions, and recall of newly learned information. Pediatric reports to date have been limited to database and single-center studies; however, a recent prospective, multicenter study of neurocognition in children with primary HTN has pointed out challenges and opportunities in designing studies to evaluate cognition in the setting of pediatric

HTN (Lande et al. 2013). The practical implications of the potential neurocognitive deficits associated with HTN in childhood are not clear. It is even less clear whether there would be any implications for longer-term cognitive reserve and ultimate cognitive decline in later life (Kupferman et al. 2013).

There are currently no association studies relating organic brain lesions or subtle neurocognitive impairment with ABP values, although in some recent studies concerning the relation between HTN and neurocognitive dysfunction the assessment of HTN can use ABPM in order to avoid including participants with white-coat hypertension (Lande et al. 2015, 2017).

## Conclusions

The introduction of ABPM with the use of automatic devices that record BP during regular life activities have collected information that permitted better understanding of circadian BP behavior and its role in the pathophysiology of the HTN-induced TOD. Both the 2016 ESH and 2017 American pediatric hypertension guidelines recommend the use of ABPM in the evaluation of early TOD as an important step in a risk stratification strategy. Further, those recommendations suggest repeated ABPM assessment in follow-up. The relation between TOD in the heart and the kidney and ABP values usually is more accurate as compared to those observed with office BP. In addition, abnormalities in circadian BP variability observed with 24-h ABPM have also been linked with the presence of organ damage. Future studies will likely expand the knowledge about the relevance of ABP in the natural history of HTN.

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Carissa M. Baker-Smith and Nicholas Pietris

## Abstract

Exercise testing is routinely performed to assess functional capacity, identify changes in cardiopulmonary physiology, evaluate symptoms and signs induced by exercise, and to determine the appropriateness of physical activity in children (and adults) with acquired and congenital heart disease. In this chapter, we summarize the basics of exercise testing, discuss what is known regarding the utility of exercise testing in the evaluation of the hypertensive child, and review existing recommendations regarding exercise testing and competitive sports participation in the hypertensive athlete.

## Keywords

Hypertension • High blood pressure • Pediatric • Child • Activity • Exercise • Exercise recommendations

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## Introduction

At least 1% to 5% of children living in the United States are hypertensive (Ahern and Dixon 2015; de Moraes et al. 2014). The most common risk factor for hypertension among youth is obesity (Aguilar et al. 2010; Sorof et al. 2004). Participation in regular physical activity has been shown to help prevent obesity and effectively reduce the

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body mass index (BMI) of obese children (Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report, 2011, Kelley et al. 2015). Additionally, higher levels of cardiopulmonary fitness are associated with a reduced risk of developing hypertension.

Hypertension is not only common among obese children; many nonobese athletes are also hypertensive (Karpinos et al. 2013). This chapter examines the impact of exercise on blood pressure and the utility of exercise testing within the pediatric population. Finally, we will examine recommendations for exercise participation, including competitive sports participation, in hypertensive youth.

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### **The Basics: Measurements and Interpretation of the Exercise Stress Test**

The exercise stress test is a controlled and monitored method for assessing the body's response (e.g., heart rate and blood pressure) to physical stress. The stress test is typically performed in a controlled setting and staffed by a cardiologist and exercise physiologist.

The performance of exercise stress tests relies on the use of an ergometer. Examples of ergometers frequently employed include the cycle ergometer and the treadmill. Interpretation of data from the exercise stress test involves using established exercise protocols for assessing one's physiologic response to exercise and determining whether the responses are appropriate for age and gender. Key variables such as heart rate (HR), blood pressure, and oxygen consumption (VO<sub>2</sub>) are frequently assessed (see Table 1). Protocols, such as the Bruce protocol, provide normative values by age and allow for assessments of appropriate endurance time, peak HR, and blood pressure. Qualitative measures such as "perceived exertion" and "reason for end of test" are also recorded during routine exercise stress testing (Paridon et al. 2006).

Cardiac output is the product of stroke volume (SV) and heart rate (HR). During exercise, as

during other times of stress (e.g., orthostatic, environmental, etc), HR increases to maintain required cardiac output. Maximum heart rates are assessed during routine stress testing.

Blood pressure is also routinely assessed prior to the start of the exercise stress test, throughout the testing, and during the recovery period. The accuracy and consistency of blood pressure measurements obtained by trained staff are essential to the generation of clinically useful data. Guidelines have described the equipment and manner in which blood pressure measurements should be obtained (Paridon et al. 2006). The equipment should include a blood pressure cuff size in which the bladder encircles and covers at least 80–100% of the arm length with a width that covers at least 40% of the arm circumference at the midpoint (Falkner and Daniels 2004). A validated digital manometer or a calibrated aneroid sphygmomanometer should be utilized. A stethoscope is utilized to appreciate the Korotkoff sounds. Phase I should be recorded as the systolic blood pressure (SBP). Phase V, coinciding with the disappearance of Korotkoff sounds, should be recorded as the diastolic blood pressure (DBP). However, it is important to note that use of the pressure corresponding to Korotkoff Phase IV (e.g., the onset of muffling of the heart sounds) may be required in some children if Korotkoff sounds continue to be appreciated until the manometer reaches 0 mmHg (Perloff et al. 1993).

Blood pressure (BP) is the product of peripheral vascular resistance (PVR) and cardiac output (CO). PVR is determined at the arterial level. During exercise, due to a variety of mechanisms, the vascular beds dilate. As a result, there is a decline in PVR. However, the increase in CO that occurs during peak activity is out of proportion to the decrease in peripheral resistance, resulting in an increase in SBP during peak activity.

Low blood pressure, during peak activity, can be a sign for concern. Measurements of low blood pressure during peak activity and failure of the blood pressure to increase during peak activity have been associated with significant left ventricular outflow tract obstruction, insufficient preload, and compromised left ventricular systolic function (Paridon et al. 2006); Such findings are

**Table 1** Variables assessed during the cardiopulmonary exercise test (Ref: Washington et al. 1994; Godfrey et al. 1971; Paridon et al. 2006; Longmuir et al. 2013)

Variable	Measurement	Significance
Heart rate (HR)	Measured prior to, during, and post exercise. Impacted by position during exercise (e.g., standing vs. sitting), gender, state of health, and fitness of the child as well as environmental conditions (e.g., room temperature). Higher maximum HR is expected in younger children due to smaller hearts and lower stroke volume (SV) for a given rate of work. Peak HR is not impacted by degree of conditioning (although resting HR is lower in conditioned persons.)	The heart rate increases linearly with the rate of work during dynamic exercise.
Blood pressure (BP)	$BP = \text{peripheral vascular resistance (PVR)} \times \text{cardiac output (CO)}$	In children with normal cardiac function and no evidence of left ventricular outflow obstruction or compromised preload, systolic blood pressure (SBP) typically increases during peak activity. Diastolic blood pressure (DBP) has not traditionally been measured accurately during stress testing.
Oxygen consumption (VO <sub>2</sub> )	Measure of energy expenditure. A surrogate marker of the intensity of exercise. Increases rapidly with initiation of dynamic exercise. Plateaus after the 2nd minute at each level of intensity of exercise. Strongly related to body weight. Thus measures are traditionally indexed by body weight. VO <sub>2</sub> max = the greatest amount of oxygen that a given individual can consume while performing dynamic exercise. Cannot be easily measured in children. Peak VO <sub>2</sub> = the maximal amount of oxygen uptake observed during a specific exercise study (often used in place of VO <sub>2</sub> max in children).	VO <sub>2</sub> increases proportionately with the intensity of exercise, until it plateaus. VO <sub>2</sub> is higher in treadmill versus cycle ergometer use (Hermansen and Saltin 1969). VO <sub>2</sub> increases tenfold in children during exercise. A trained athlete can reach a VO <sub>2</sub> that is 20 fold the baseline.
Ventilatory anaerobic threshold (VAT)	The point at which carbon dioxide output (VCO <sub>2</sub> ) and minute ventilation (VE) begin to increase out of proportion to VO <sub>2</sub> . The VAT represents the point at which the subject's oxygen supply is out of balance with the oxygen demands of the exercise/activity.	Once the VAT is reached, tissue oxygen delivery reaches the maximum and additional energy sources are provided by glycolysis. This switch from aerobic to anaerobic metabolism at the VAT leads to a rise in muscle and plasma lactic acid.
Metabolic equivalents in exercise testing (METS)	1 MET is the amount of oxygen consumed at rest, sitting quietly in a chair. 1 MET is equivalent to 3.5 ml O <sub>2</sub> /kg/min (or 1.2 kcal/min for a 70 kg person) (Jetté et al. 1990)	The MET is a useful measurement for quantifying exercise intensity where the intensity of a particular activity is described as a multiple of the resting metabolic rate. It is estimated during stress testing and used to gauge the level of intensity reached during stress testing. 2 METS is equivalent to 7.0 ml O <sub>2</sub> /kg/min and 3METS is equivalent to 10.5 ml/O <sub>2</sub> /kg/min. In terms of practical, everyday activities and athletic activities, washing the dishes is 2.1METS; shoveling snow is 5.1 METS; bowling is 2–4METS; and figure skating is 12.9METS.

(continued)

**Table 1** (continued)

Variable	Measurement	Significance
Respiratory exchange ratio (RER)	Ratio of carbon dioxide output (VCO <sub>2</sub> ) to oxygen consumption (VO <sub>2</sub> ).	Typically the RER is less than 1. As exercise intensity increases, the RER increases. A value of >1.1 suggests that a child's effort during exercise testing has approached maximal effort and signals the onset of anaerobic metabolism.
Perceived exertion	Subjective rating of intensity of perceived exertion.	Good indicator of relative fatigue. Typically reproducible.

of low sensitivity and specificity for defining the presence of disease. However, if present, low blood pressure response during peak activity should be assessed fully.

SBP has a direct relationship to a person's age, weight, height, and body mass index (Becker et al. 2007). Children and adults with elevated baseline blood pressure tend to have proportionately higher blood pressures during peak activity. Maximum blood pressure during exercise in children rarely exceeds 200 mmHg (Washington et al. 1994). In the very hypertensive child, however, it is possible for blood pressures to exceed this value. Risks associated with more extreme elevations in blood pressure during peak activity are currently unknown. Thus, while there is no absolute BP to avoid during exercise in children that has been associated with an increased risk for death, in general, it is recommended that an exercise test be terminated if a child develops severe hypertension, defined as a SBP greater than 250 mmHg or a DBP greater than 125 mmHg; the test may also be terminated if the blood pressure can no longer be measured and there is concern for extremely elevated blood pressure based upon the highest value available during the study (Paridon et al. 2006; Washington et al. 1994). Additional signs that a test should be terminated, aside from extreme BP, include the presence of ST segment elevation of  $\geq 3$  mm on the ECG, increasing ventricular ectopy, or the onset of ventricular tachycardia (e.g., >3 consecutive premature ventricular complexes) (Paridon et al. 2006). It is also recommended that a test be terminated if the child develops symptoms of inadequate cardiac output, such as extreme fatigue or dizziness (Paridon et al. 2006; Longmuir et al. 2013).

## Indications and Contraindications for Exercise Testing

In 2006, the American Heart Association Council on Cardiovascular Disease in the Young, Committee on Atherosclerosis, Hypertension and Obesity in Youth (AHOY) published an updated report describing appropriate performance of exercise testing in children (Paridon et al. 2006). In this report, committee members noted that the role for pediatric exercise testing had expanded. Common reasons to perform pediatric exercise stress testing include: (1) evaluation of specific signs and symptoms induced or aggravated by exercise, (2) assessment and/or identification of abnormal responses to exercise in children with cardiac (e.g., arrhythmias), pulmonary, or other organ disorders; (3) assessment of the efficacy of specific medical and/or surgical treatments; (4) assessment of functional capacity in preparation for participation in recreational, athletic, or vocational activities; (5) evaluation and prognosis in children with known heart disease (or risk factor for heart disease); and (6) establishing baseline data prior to the initiation of cardiac, pulmonary, or musculoskeletal rehabilitation.

There are few absolute contraindications to exercise testing (e.g., acute myocardial injury, pericardial inflammation, and severe outflow tract obstruction). However, many conditions require caution on the part of the performing providers and careful monitoring during testing (Paridon et al. 2006). Individuals with high risk conditions, such as children with pulmonary hypertension, documented long QT syndrome,

dilated cardiomyopathy, restrictive cardiomyopathy, hypertrophic cardiomyopathy with symptoms, mild left ventricular outflow tract obstruction (LVOTO), documented arrhythmia, and unexplained syncope, are among the highest risk patients for whom the physician should remain present and on alert during stress testing (Paridon et al. 2006).

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### **Normal Blood Pressure Response to Exercise**

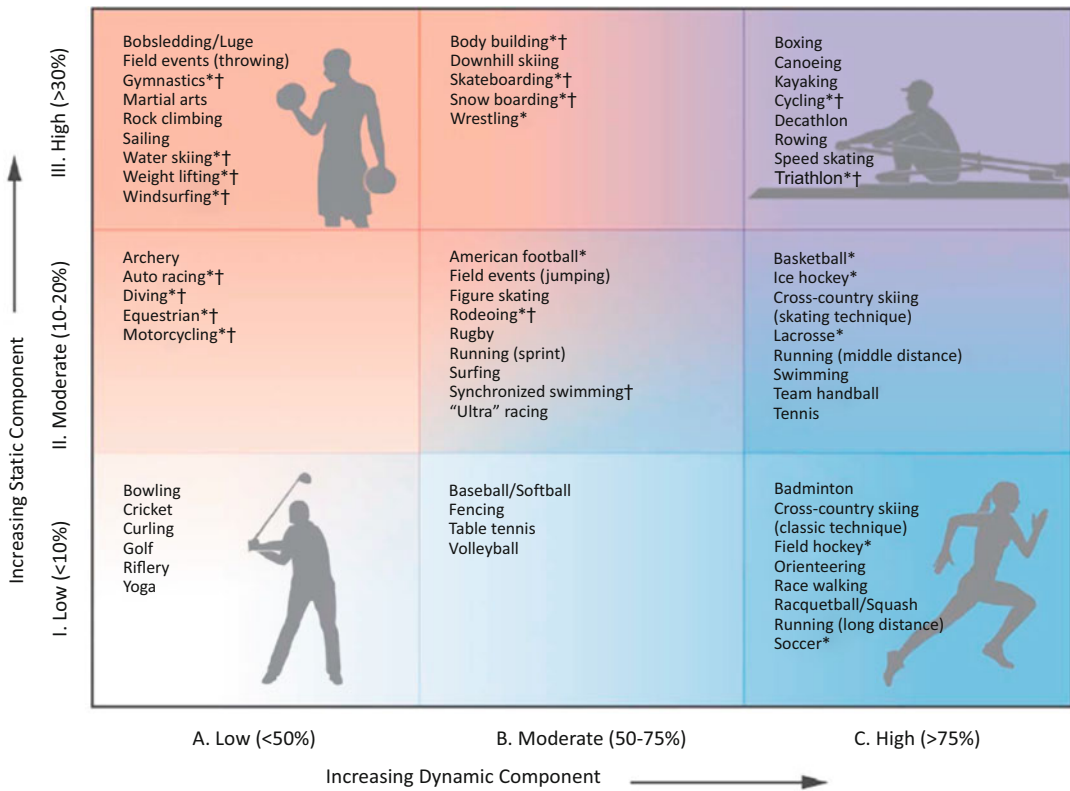
In general, exercise is a structured activity that involves repetitive motions of the body. The purpose of exercise is to maintain or improve one or more levels of physical fitness. There are various types of exercise: dynamic/aerobic, static/isometric, isotonic and isokinetic. Dynamic activity involves “joint movement through relatively small forces within the muscle” (Mitchell et al. 1994) while static activity is exercise that involves large intramuscular forces but little to no joint movement (Mitchell et al. 1994). Isotonic exercise refers to activities where the muscle shortens through a constant external load (i.e., equal tone). Isokinetic exercise involves lengthening (or shortening) of the muscle at a constant velocity.

Normal blood pressure response during dynamic exercise (e.g., swimming, running, cycling) is an increase in SBP due to a disproportionate increase in cardiac output versus decline in peripheral vascular resistance (Paridon et al. 2006). In contrast, the blood pressure response to static/isometric exercise (e.g., weightlifting, etc.) is a smaller increase in CO but a greater increase in mean arterial pressure (MAP). In isometric activity, the degree of increase in MAP is proportional to the muscle mass involved, the duration of the contraction, and the percentage of maximal muscle tension (Braden and Strong 1990; Buck et al. 1980, Mitchell et al. 1980, 1981; Seals et al. 1983). In general, most exercises are not solely dynamic or static (see Fig. 1: taken from ACC Task Force), but include a combination of dynamic and static activity.

### **Blood Pressure Response to Exercise in Pediatric Subpopulations**

Exercise testing can play an important role in our understanding of how the body responds to stress. Age and BMI have been shown to be predictors of exaggerated blood pressure response to exercise stress testing (de Lima et al. 2012). With regard to the diagnosis of hypertension, stress testing can also be used to determine a person’s likelihood of developing hypertension (Matthews et al. 1998; Lima et al. 2013). Exercise testing elicits responses of the body not present at rest (Washington et al. 1994). For instance, it has been well established that adults with risk factors for premature cardiovascular disease have abnormal blood pressure response to exercise, even when resting blood pressures are normal. In particular, adults with risk factors for premature cardiovascular disease such as obesity, dyslipidemia, and diabetes who have a normal or near normal resting blood pressure have been found to have marked elevation in BP during peak activity (Miyai et al. 2002; Matthews et al. 1998). In a case-control study of 151 men later diagnosed with hypertension versus 200 controls, the presence of an exaggerated response to exercise, defined as an increase in SBP >60 mmHg after 5 minutes of exercise or increase in SBP >70 mmHg after 10 min of exercise, was associated with a 2.4 times greater odds of developing systemic hypertension (Matthews et al. 1998). Similarly, in a study of 1033 Japanese men without preidentified cardiovascular disease, undergoing routine exercise stress testing as a part of a biannual physical examination, men with exaggerated exercise related BP response within the highest quartile were 3 to 4 times more likely to develop hypertension (Miyai et al. 2002).

Children with risk factors for premature cardiovascular disease also display abnormal BP response during peak activity. In fact, it has been argued that exercise BP may be a more reliable parameter of one’s true blood pressure given the opportunity for a lesser impact of psychological stress on measured blood pressure (i.e., white coat hypertension). Details regarding the relationship between risk factors for premature cardiovascular



**Fig. 1** Classification of sports activities by degree of peak dynamic and static components (Ref: Levine et al. 2015)

disease and changes in peripheral vascular resistance have also been previously described (Kavey et al. 1997; Treiber et al. 1991). In particular, children with severely increased LDL cholesterol have a significantly higher postexercise systolic and diastolic blood pressure (Kavey et al. 1997). Similarly, children with a family history of coronary artery disease exhibit higher increases in systolic blood pressure during peak activity (Treiber et al. 1991).

**Obese Children**

Obesity is very common among children and adolescents. Among children 2 to 17 years of age, the prevalence of obesity has remained fairly stable at 17% (<https://www.cdc.gov/obesity/data/childhood.html>). According to data from the Houston Screening Project, obese, inactive youth are at greatest risk for the development of systemic

hypertension (Sorof et al. 2004), but can benefit greatly from increased physical activity.

Recommendations for reducing the prevalence of childhood obesity, and thus the risk of hypertension, include dietary modifications, but also a greater reliance on physical activity (The sixth report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure 1997; García-Hermoso et al. 2013; Fife-Schaw et al. 2014). In fact, current data confirms the benefit of regular physical activity on body mass in children. A recently published systematic review of randomized controlled trials conducted between January 1, 1990, and December 31, 2012, evaluated the impact of exercise on body mass index among 971 obese children, 2 to 18 years of age participating in structured physical activity programs (e.g., aerobic training, strength training, both) for at least 4 weeks. The primary outcome measure was a change in BMI (mg/m<sup>2</sup>) following exercise



participation. Secondary outcome measures of change in body weight, percent body fat, fat mass and fat-free mass, maximum oxygen consumption in ml/kg/min (VO<sub>2</sub>max), upper and lower body strength, and kilocalorie intake were also assessed. A significant reduction in body mass index (3.6%; mean of 1.08 kg/m<sup>2</sup>) was observed among participants pre- and post-exercise participation (Kelley et al. 2015). Thus, participation in structured physical activity programs has the potential to reduce the BMI of nearly 13 million obese children living in the United States. Additional meta-analyses conducted during earlier periods have also supported these findings (Maziekas et al. 2003).

Similar to nonobese children, stress testing may be carried out in obese children for a variety of reasons including for the evaluation of exercise related chest pain, fatigue, and shortness of breath. Studies suggest that obese children have significantly lower exercise capacity compared to lean children (de Sousa et al. 2009). Obese youth exhibit adaptive changes in cardiac structure, output, and VO<sub>2</sub> in proportion to the degree of obesity. In a study of 35 boys, ages 10–12 years of age, progressive and maximal exercise testing was conducted on a bicycle ergometer in a semi-supine position, after a 3 min warm up period at 30 W, followed by incremental increases of 15 W every 3 min. Children with the highest degrees of obesity had higher baseline BMI, SBP, and DBP. During exercise, obese children achieved similar maximum heart rate but had greater stroke volume and thus generated greater CO. However, cardiac index (CI), defined as CO indexed for BSA, was no different. Similarly, although VO<sub>2</sub> is highly correlated with fat-free body mass and is highest in obese children (Sorof et al. 2004), VO<sub>2</sub> indexed by body weight was also similar in lean versus obese children (Schuster et al. 2009). This study also found that significant cardiac remodeling occurred in obese versus nonobese children (e.g., increased left atrial dimension, increased left ventricular end-diastolic diameter and increased LV mass). In general, obese children experience significant alterations in cardiac response to exercise. While these responses are initially adaptive, these compensatory changes

become maladaptive and contribute to cardiac damage as the degree of obesity increases. What begins as a hyperkinetic, adaptive response to exercise evolves to result in deterioration in systolic and diastolic myocardial function, as indicated by a decline in shortening fraction (SF) and an increase in diastolic and systolic ventricular diameter in the most obese children (Schuster et al. 2009).

### **Prehypertensive and Hypertensive Children**

Early data from the Muscatine study demonstrated that similar to normotensive youth, blood pressure also increases during exercise for prehypertensive and hypertensive youth. Blood pressure increases in proportion to the degree of resting blood pressure, such that children with prehypertension (i.e., elevated blood pressure) and hypertension demonstrate more marked increase in blood pressure response during peak activity (Schieken et al. 1983). Intensive cardiopulmonary training, however, may reduce the degree of exercise-related hypertension, even among persons with a family history of hypertension (Shook et al. 2012).

### **Children with Dyslipidemia**

Exaggerated blood pressure response to exercise has also been demonstrated in children with increased LDL cholesterol (Kavey et al. 1997). In a two-part, retrospective case-control study of 32 boys >10 years of age with LDL cholesterol  $\geq 160$  mg/dL and a prospective case-control study of 10 hypercholesterolemic boys with LDL cholesterol >160 mg/dL, at the end of a 10 minute recovery period, SBP remained significantly higher in the high LDL group (mean SBP of 121 mmHg versus 111 mmHg,  $p < 0.001$ ). The study also found an exaggerated SBP and DBP response to exercise in children with hypercholesterolemia. Theories regarding the exaggerated blood pressure response during and following exercise include increased arterial pulse-wave

velocity (PWV), reduced arterial elasticity, and exaggerated flow pulse-wave transmission (Kavey et al. 1997).

### **Children with Impaired Glucose Tolerance/Type 2 Diabetes**

Limited data in children has suggested that the presence of type 2 diabetes mellitus (T2DM) results in compromised exercise performance (Yardley et al. 2015). In a small case control study of normal weight, obese, and T2DM children, obese children and children with T2DM were able to complete less work, as measured by peak work rate (Watts), but reached the same peak heart rate as the nonobese children. VO<sub>2</sub> max, an indicator of cardiopulmonary reserve, endurance capacity, and exercise fitness, was also lower in obese and T2DM children (Nadeau et al. 2009).

In a comparison between type 1 diabetes mellitus (T1DM) and T2DM female adolescents, those with T2DM had a lower maximal aerobic capacity. Both groups had reduced aerobic capacity compared with the nondiabetic control group (Gusso et al. 2008).

### **Children of Parents Who Smoke**

Environmental and familial risk factors have been associated with elevated blood pressure response to exercise in children. Parental obesity, smoking, and low educational level, as well as a positive family history of hypertension, have all been associated with enhanced blood pressure response to exercise in adolescents (Hacke and Weisser 2015). Exposure to parental cigarette smoke has been associated with elevated blood pressure in children and an abnormal response to exercise. A cross-sectional study of 492 children from Kiel, Germany, enrolled in the Kiel Ex Press study found modest correlations between resting and exercise SBP after adjusting for age, sex, and height among children exposed to parental cigarette smoke. Exposure to parental cigarette smoke was associated with a significantly

increased SBP during exercise (+6.3 mmHg,  $p < 0.001$ ). A history of parental hypertension and familial hypertension was also associated with higher resting BPs. Parental inactivity was associated with significantly higher exercise systolic blood pressure.

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### **Congenital Heart Disease: Resting Blood Pressure and Blood Pressure Response During Exercise**

Exercise is beneficial to maintaining the health and well-being of all children, including children with congenital heart disease (CHD) (Longmuir et al. 2013; Kaminer et al. 1995). Historically, exercise testing has served not only as a means for assessing exercise capacity in persons with congenital heart disease (CHD) but also as a method for predicting long-term outcome (Inuzuka et al. 2012).

### **Coarctation of the Aorta**

Coarctation of the aorta, defined as the presence of discrete narrowing within the descending aorta, is the most common cardiac cause of systemic hypertension. Children with a history of aortic coarctation repair, even without residual obstruction, are at risk for persistent or recurrent hypertension (Hager et al. 2007; Presbitero et al. 1987; Bhat et al. 2001; Madueme et al. 2013). While there is some debate regarding the best predictors of the need for additional intervention (Ou et al. 2004; Engvall et al. 1995), exercise testing has been evaluated as a means for eliciting the presence of arm-leg blood pressure gradient in children with repaired coarctation of the aorta even in the absence of a resting gradient. In a retrospective case-control study of 33 subjects with repaired coarctation of the aorta and normal resting blood pressure gradient, children with a history of coarctation had a mean increase in BP arm-leg gradient of 42  $\pm$  30 mmHg (range 2 to 110 mmHg) with exercise ( $p < 0.0001$ ) versus a mean arm-leg gradient of 5  $\pm$  5 mmHg seen in normal children (Markham et al. 2004).

## Exercise Recommendations in Hypertensive Athletes

In general, it is recommended that children participate in 60 min or more of physical activity per day at least 3 days per week. Moderate to high energy activity is preferred (Longmuir et al. 2013). Participation in physical activity has been shown to result in a decrease in SBP and DBP (Farpour-Lambert et al. 2009). Due to limited data regarding the impact of LV mass on sudden death risk in children (without a known cardiomyopathy), there are no clearly defined guidelines regarding exercise participation in the athlete with LVH (Alpert 1999). The American Academy of Pediatrics has recommended avoiding heavy weight lifting, power lifting, and bodybuilding and high-static component sports among youth with uncontrolled hypertension (Rice 2008). A recent AHA/ACC Scientific Statement provides guidance for exercise recommendations for hypertensive athletes (see Table 2).

Competitive athletic activity refers to participation in an organized team or individual sport that requires regular competition against others as

a central component, places a high premium on excellence and achievement, and requires some form of systematic (and usually intense) training (Graham et al. 2005).

Observational studies suggest that the prevalence of sudden cardiac death (SCD) in athletes 12 to 35 years of age is 2.3 per 100,000 per year (Maron et al. 1998). Cardiovascular screening of athletes and nonathletes is complex and evolving (Maron et al. 1998, 2016). The risk of sudden death among an athlete with hypertension does not appear to be any greater than that of a non-hypertensive athlete, such that treatment of the hypertension does not result in a decline in the rate of sudden death (Taverny et al. 2016). However, exercise represents a high dynamic state associated with increased myocardial oxygen demand. Patients with uncontrolled hypertension may have left ventricular hypertrophy. There is no data to convincingly demonstrate that the presence of LVH in a hypertensive athlete places the athlete at greater risk for sudden death. However, arguably, the physiology would suggest that if during maximum exercise the cardiac output increases fourfold and that (as has been shown)

**Table 2** AHA/ACC scientific statement exercise recommendations for hypertensive youth (Black et al. 2015)

	Recommendation
1	It is reasonable that the presence of stage 1 hypertension in the absence of target-organ damage should not limit the eligibility for any competitive sport. Once having begun a training program, the hypertensive athlete should have BP measured every 2 to 4 months (or more frequently, if indicated) to monitor the impact of exercise (Class I; level of evidence B)
2	Before people begin training for competitive athletics, it is reasonable that they undergo careful assessment of BP, and those with initially high levels (>140 mmHg systolic or >90 mmHg diastolic) should have comprehensive out-of-office measurements to exclude errors in diagnosis. Ambulatory BP monitoring with proper cuff and bladder size would be the most precise means of measurement (Class I; level of evidence B).
3	Those with prehypertension (BP of 120/80 mm Hg–139/89 mm Hg) should be encouraged to modify their lifestyles but should not be restricted from physical activity. Those with sustained hypertension should have screening echocardiography performed. Athletes with LVH beyond that seen with “athlete’s heart” should limit participation until BP is normalized by appropriate antihypertensive drug therapy (Class IIa; level of evidence B).
4	It is reasonable that athletes with stage 2 hypertension (a systolic BP >160 mmHg or a diastolic BP >100 mmHg), even without evidence of target-organ damage, should be restricted, particularly from high static sports, such as weight lifting, boxing, and wrestling, until hypertension is controlled by either lifestyle modification or drug therapy (Class IIa; level of evidence B).
5	When prescribing antihypertensive drugs, particularly diuretic agents, for competitive athletes, it is reasonable for clinicians to use drugs already registered with appropriate governing bodies and if necessary obtain a therapeutic exemption (Class IIa; level of evidence B).
6	When hypertension coexists with another cardiovascular disease, it is reasonable that eligibility for participation in competitive athletics is based on the type and severity of the associated condition (Class IIa; level of evidence C).

the rise in SBP and mean arterial pressure (MAP) increases fourfold, then the myocardial demand for oxygen would also increase significantly (Braden and Strong 1990). Combined with compromised coronary artery perfusion pressure, increased myocardial oxygen demand could increase the risk of stress related myocardial injury.

A Finnish prospective cohort study of 2682 adult male volunteers, 42 to 61 years of age, found that among those with LV mass within the top quartile ( $LVM > 120 \text{ gm/m}^2$ ) in comparison to those with LV mass within the bottom quartile ( $LVM < 89 \text{ gm/m}^2$ ), that the hazard ratio for a SCD event was 2.57:1 (95% CI: 1.24 to 5.31;  $p < 0.001$ ). Of the 63 reported cases of SCD, over the 20.2 year follow-up period, LV mass was a significant predictor of SCD risk (Laukkanen et al. 2014). Potential explanations proposed by the authors included a greater risk for electrophysiological alterations induced by the increased LV mass resulting in a greater risk for arrhythmia related sudden death, lower coronary-flow reserve in the setting of increased oxygen requirements, reduced endothelial vasodilatory capacity resulting in impaired LV muscle filling and contractility.

Left ventricular hypertrophy is a known complication of uncontrolled blood pressure. However, alterations in the left ventricular dimension are also a known manifestation of the athletic heart (Caselli et al. 2014). While the development of LVH can occur secondary to hemodynamic factors (e.g., blood pressure, artery structure and stiffness, and volume load), non-hemodynamic factors such as the sympathetic nervous system and the renin-angiotensin-aldosterone system also play a role. LVH can develop through a process of cardiomyocyte hypertrophy, resulting in impaired systolic contractility and diastolic dysfunction (Kahan and Persson 2015). Compromised diastolic function leads to impaired coronary artery flow reserve. This compromised flow reserve may lead to myocardial injury and fibrosis with resultant increased risk for arrhythmia, especially during peak activity. Thus, while theoretical in children, an argument can be made that maximum activity in the

setting of left ventricular hypertrophy is a recipe for myocardial ischemia, arrhythmia, and, potentially, sudden death. At the present time, there are no established protocols or recommendations for assessing myocardial injury related to LVH in the hypertensive athlete. Furthermore, although hypertension is a major etiologic risk factor for heart failure (Levy et al. 1996), the mechanisms involved in the transition from hypertensive heart disease to heart failure are not completely understood and even less well understood in younger persons (Kahan and Persson 2015).

Despite the lack of conclusive data regarding the risk of sudden death among hypertensive athletes, limited data suggest that racial differences may exist. It has been reported that sudden death among black athletes is higher than rates of sudden death among white athletes (Reinier et al. 2015). Higher rates of diabetes (52% vs. 33%), hypertension, and chronic renal insufficiency were also reported among black versus white athletes (Reinier et al. 2015). Finally, higher rates of hypertrophic cardiomyopathy were also noted among black versus white athletes (Reinier et al. 2015).

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## Hypertensive Athlete and Athletic Performance

It has been demonstrated that hypertensive athletes have reduced exercise capacity compared to their nonhypertensive counterparts. Physiologic parameters such as increased resting heart rate and heart rate reserve in hypertensive athletes were also associated with impaired maximal oxygen consumption ( $VO_2 \text{ max}$ ). This suggests a complex interaction of cardiovascular performance indicators among those with elevated blood pressure. Hypertension that is poorly controlled may be a risk factor for future cardiovascular risk and poor exercise performance, particularly among athletes. Further research is needed in this regard to understand the effects of hypertension in pediatric patient populations and their long-term risks of cardiovascular events (Mazic et al. 2015).

## Conclusions

In summary, hypertension is recognized as a key risk factor for cardiovascular disease. Exercise stress testing helps us understand the physiologic responses to exertion. There are multiple ways that stress testing can contribute to patient care. It may be utilized to help “clear” a patient who is experiencing exercise intolerance but who wishes to or may benefit from being engaged in a more rigorous exercise program. Exercise stress testing serves as an objective measure of one’s fitness level longitudinally to help understand the impact of disease progression (i.e., diabetes, obesity, etc.). It may also help protect those from potential harm and exclude them for particular activities such as those with stage 2 hypertension and signs of end-organ damage. Importantly, the development of hypertension and the progression from prehypertension to hypertension is a complex, multifactorial process. Understanding the pediatric patient’s physiologic response to this milieu of vascular and hormonal factors will help us further define the pathogenesis and risk factors surrounding this transition and to improve the care we provide our patients.

## Cross-References

- ▶ [Development of Blood Pressure Norms and Definition of Hypertension in Children](#)
- ▶ [Ethnic Differences in Childhood Blood Pressure](#)
- ▶ [Hypertension in Children with Type 2 Diabetes or the Metabolic Syndrome](#)
- ▶ [Obesity Hypertension: Clinical Aspects](#)
- ▶ [Renovascular Hypertension, Vasculitis, and Aortic Coarctation](#)
- ▶ [Secondary Forms of Hypertension in Children: Overview](#)

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## Abstract

The treatment of blood pressure elevation once it is recognized is quite important. The first line of treatment for children with either elevated blood pressure or hypertension is nonpharmacologic treatment. In fact, a meaningful trial of nonpharmacologic approaches is always important before considering using medication.

Nonpharmacologic treatment largely focuses on weight management, changes in diet and increased physical activity. For children and adolescents who are overweight or obese, improvement in the body mass index (BMI) percentile can be effective in lowering blood pressure and may be the most important aspect of blood pressure management. Dietary modifications that include reduction of overall calories, as well as reduction of sodium, have been shown to reduce blood pressure in some individuals. The Dietary Approaches to Stop Hypertension (DASH) diet is also helpful in management of hypertension. Finally, increasing physical activity, particularly

aerobic physical activity, can lower blood pressure even when increased physical activity does not result in weight loss. Health care providers must learn approaches to behavior change that help patients and their families modify their diet and activity behaviors.

## Keywords

Diet • Physical activity • Behavior change • Weight management • Obesity • Sodium

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## Introduction

Nonpharmacologic treatment of hypertension is important in the pediatric age range. There is emerging information showing that weight management for those who are overweight or obese – changes in diet to reduce sodium and foods high in

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saturated fat or added sugar, while increasing whole grains, low-fat dairy, fruits and vegetables, as well as increasing physical activity – can be effective in lowering blood pressure. It is important for health care providers to understand and be able to implement the nonpharmacologic approaches to treat hypertension.

Nonpharmacologic approaches to the treatment of hypertension should be the first line of approach in children and adolescents with blood pressure elevation and stage 1 hypertension. Patients in these categories should have a period of treatment with lifestyle changes before pharmacologic intervention is considered. Usually, this means 6 months of meaningful attempts at behavior change in both diet and physical activity. Even when the decision is made to use medication to treat hypertension, it is important to continue the nonpharmacologic intervention as this may allow lower doses or fewer medication to reach blood pressure goals.

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## Sodium

Diet is one of the major determinants of blood pressure. Dietary salt and its main constituent, sodium, is one of the most studied nutrients in this regard as it plays a central role in regulating fluid balance in the body. In children, as in adults, excessive sodium intake leads to blood volume expansion and can potentially lead to the development of arterial hypertension (Lava et al. 2015). A positive relationship between salt intake and hypertension in children has been demonstrated in observational and population studies (He et al. 2008; Yang et al. 2012). A pooled analysis of nine randomized controlled studies of reduced-salt diets compared to usual intake showed significant blood pressure lowering in children (He and MacGregor 2006). Median salt intake reduction was 42% over 4 weeks in this analysis; this reduction was accompanied by an average systolic blood pressure lowering of 1.17 mmHg and a diastolic blood pressure lowering of 1.29 mmHg. In a pooled analysis of three intervention trials in infants, a 54% median net reduction in salt over 20 weeks was associated with an average decrease

in systolic blood pressure of 2.47 mmHg (He and MacGregor 2006). For infants, breast milk on average has lower sodium content than formula along with many other nutritional benefits (Hazebroek and Hofman 1983). Exclusive breast-feeding for the first 6 months of life has been associated with early cardiovascular benefits including lower blood pressure (Brion et al. 2008; Horta and Victora 2013), lower cholesterol levels, and lower body mass index (BMI) compared to formula-fed infants (Demmers et al. 2005; Parikh et al. 2009). The Surgeon General's Office, the World Health Organization, the American Academy of Pediatrics, and the American Academy of Family Physicians recommend exclusive breastfeeding through the first 6 months of life for this and other reasons.

Salt intake increases with age as total food consumption and food choice increase (Brown et al. 2009). Much of the salt in the infant diet comes with the introduction of solid foods at ~6–9 months of age. Older children consume ~80% of their salt intake from manufactured foods, snacks, and restaurant and fast-food meals, whereas ~10% occurs naturally in foods and 10% comes from discretionary salt use at home (Carriquiry et al. 2013). Introducing children to unprocessed and no- or low-sodium forms of foods early in childhood, when eating habits are being formed, is an important step in preventing the age-associated rise in sodium intake. When the need arises, replacing regular versions of packaged foods with no or low sodium varieties would be another useful strategy to lower the sodium content of children's diets. In addition, foods cooked from scratch are naturally lower in sodium than most instant and boxed meals and take-out foods. To aid in sodium reduction, families should be assessed for their food literacy and counseled accordingly on food shopping skills and their ability to read food labels, cook, and flavor foods using low sodium methods (Appel et al. 2015).

School-based salt-reduction interventions have yielded favorable changes to children's sodium intake and blood pressure. As evidence, in the Andover-Exeter Project (Ellison et al. 1989), sodium was significantly reduced in the school meals; for those students who relied on the school

for their meals, sodium intake and blood pressure were significantly reduced after 2 years. Children who eat school meals can consume 50% or more of their daily calories at school (Stallings et al. 2010). Therefore, it is important that foods available in school meals meet sodium and other nutrient recommendations that promote the development of heart healthy eating habits. Federally funded school breakfast and lunch programs are currently operating under the Healthy Hunger-Free Kids Act (HHFKA) (Food and Nutrition Service 2016). This program includes a step-wise plan to reduce sodium levels in school meals by approximately 50% by 2022. The ultimate goal of HHFKA is to help children achieve daily sodium targets set by the Institute of Medicine (Institute of Medicine 2005), which are 1900 mg/day for children ages 4–8 years, 2200 mg/day for children 9–13 years, and 2300 mg/day for adolescents 14–18 years. These goals are consistent with the 2015 Dietary Guidelines for Americans (Dietary Guidelines Advisory Committee 2015). For children with hypertension, the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents recommends that sodium intake be kept to 1200 mg/day for 4–8-year-olds and 1500 mg/day for older children (National High Blood Pressure Education Program 2004). Some people with hypertension show a greater decrease in their blood pressures in response to reduced sodium intake than others. The term sodium-sensitive hypertension has been used to identify these individuals. In general, children and adolescents who are sensitive to the effects of salt and sodium tend to be those who are African-American, overweight or obese, or have diabetes or have a family history of hypertension (Yang et al. 2012). Unfortunately, at present, there is no practical approach to determining sodium sensitivity for use in a clinical setting.

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## Dietary Patterns

Single nutrient studies of potassium, calcium, and magnesium, as well as dietary fiber, have shown favorable effects on blood pressure in youth,

although the evidence is conflicting (Lande and Kupferman 2013; Torrance et al. 2007). The Dietary Approaches to Stop Hypertension (DASH) dietary pattern was developed to optimize the potential synergistic effect of these nutrients when combined (Appel et al. 1997). The DASH diet emphasizes foods rich in potassium, calcium, magnesium, and fiber for lowering blood pressure, while minimizing nutrients associated with elevated blood pressure, such as saturated fat. Per 2000 calories, the DASH diet recommends 7–10 servings/day of fruits and vegetables, 2–3 servings/day of low-fat or nonfat dairy, 7–8 servings/day of mostly whole grains, a weekly serving of beans and nuts, 2 or less servings/day of lean meats, fish, and poultry, and limited intake of foods high in fat, sugar, and sodium. Couch et al. (2008) showed that adolescents with prehypertension and hypertension could achieve a significant reduction in systolic blood pressure in response to a 3 month behaviorally oriented nutrition intervention emphasizing a DASH-type diet compared to usual hospital-based nutrition care. The relative change in systolic blood pressure in this study was  $-7.9\%$  in the DASH diet group compared to  $-1.5\%$  in the usual care group, which was significantly different.

The components of the DASH diet, specifically fruits, vegetables, and low-fat dairy foods, have been examined in relation to their blood pressure lowering potential in children (Moore et al. 2005, 2012) showed that girls 9–10 years of age who consumed two or more servings of dairy per day experienced a 33% reduced risk of elevated blood pressure late in adolescence compared to those who did not. The combined intake of both dairy products and fruits and vegetables (DASH-type diet) resulted in a 36% reduction in the risk of high blood pressure in late adolescence. This effect was not observed with increased fruit and vegetable intake alone. Similar beneficial effects of a DASH-type dietary pattern have been observed in children. The Framingham Children's Study showed that children who consumed higher intakes of fruits and vegetables ( $\geq 4$  servings/day) plus dairy products ( $\geq 2$  servings/day) in their preschool years had a smaller age-associated increased in systolic and diastolic

blood pressure throughout childhood than children who consumed less of these foods, even after adjusting for BMI (Moore et al. 2012).

Because many children with elevated blood pressure are also overweight, DASH-focused interventions, combined with physical activity education, have been studied when targeted to overweight youth. In the Pacific Kids DASH for Health (PacDASH) study, tailored computer-generated messaging grounded in behavioral change theory was used to encourage active play and compliance to a DASH diet (Novotny et al. 2015). Through diet and physical activity modification, the aims of PacDASH were to achieve weight and blood pressure maintenance among Pacific Islander children who were in the upper half of the BMI distribution; this compared to an attention matched control group. While no differences in weight status were observed posttreatment, PacDASH participants showed greater fruit and vegetable consumption and a 12 unit lower diastolic blood pressure compared to the controls after 9 months. Nourse et al. (2015) tested a live video conferencing-based intervention emphasizing a DASH eating plan combined with a moderate intensity physical activity program on reducing blood pressure and improving measures of cardiovascular health in obese children. Results of this telehealth delivery approach showed a high level of adherence among participants and significant favorable changes in vascular endothelial function and arterial stiffness indices after 3 months. Given that low dietary adherence often impedes the success of many lifestyle interventions among youth (Skelton and Beech 2011; Oude Littikhuis et al. 2009), telehealth delivery approaches show promise as a means of increasing access to lifestyle interventions to improve health and modify behavior in children.

Overall, these studies support the use of a DASH-type dietary pattern as a means of lowering blood pressure in a hypertensive pediatric population. When combined with behavior modification strategies and moderate intensity physical activity, a DASH-focused intervention has the potential to improve cardiovascular health in overweight youth. Current guidelines for blood pressure management in children suggest that all children, and hypertensive youth in particular, can

benefit from a dietary increase in fresh vegetables, fresh fruits, fiber, and nonfat dairy (Flynn et al. 2017; National High Blood Pressure Education Program 2004). Clinicians should counsel patients on how to implement this diet and recognize certain barriers, such as cost, and discuss approaches to overcome these barriers. Registered dietitians can be quite helpful in the implementation of this dietary approach.

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## Physical Activity

Epidemiologic studies have consistently demonstrated a relationship between physical activity and blood pressure in both adults and children. The relationships suggest that increased levels of physical activity are associated with lower blood pressure. Sallis et al. found in a study of young adults that the level of physical activity was inversely related to diastolic blood pressure (Sallis et al. 1986). A large epidemiologic study in a rural community in China showed that, in adolescents and young adults, physical activity dampens the blood pressure increase observed with a diet high in sodium (Rebbhooz et al. 2012). In longitudinal studies, low levels of physical activity have been associated with higher rates of development of hypertension (Blair et al. 1984). In children, Gidding et al. (2006) showed that higher self-reported physical activity was associated with lower systolic blood pressure.

There have also been interventional studies focused on physical activity and blood pressure. A review of nine interventional studies in obese children and adolescents showed that approximately 40 min of moderate-to-vigorous physical activity performed 3–5 days per week is associated with both improved systolic blood pressure and vascular function (Torrance et al. 2007). Moderate physical activity is associated with increased heart rate and respiratory rate. During moderate physical activity, one can talk, but not sing. Vigorous physical activity is associated with higher heart and respiratory rate and the child can neither talk nor sing at this level of physical activity. Farpour-Lambert et al. (2009) demonstrated that 3 months of increased physical activity, including

three 60-min aerobic and strengthening sessions a week, lowered both office-measured blood pressure and 24-h systolic blood pressure.

There have also been studies evaluating the effect of different forms of physical activity on blood pressure. Aerobic exercise is defined as exercise that is usually rhythmic, involving use of large muscle groups, which results in increased heart and respiratory rate. Examples of aerobic activity include walking, running, cycling, and swimming. Resistance training includes activities such as weight training where the goal is loading specific muscle groups with increased resistance, sometimes to the exhaustion of that muscle group via prolonged exposure or repetitive exposures. A randomized controlled clinical trial of aerobic activity compared to resistance training, combined training, or a nonexercise control group showed reductions in systolic and diastolic blood pressure in both the aerobic exercise and the strength training groups (Cai et al. 2014). A meta-analysis of 12 clinical trials found reductions of 1% and 3% for resting systolic and diastolic blood pressure respectively in response to physical activity (Kelley et al. 2003).

The studies of resistance activity show a reduction of systolic blood pressure from 3 to 6 mmHg. The studies of aerobic exercise have included individuals with normal blood pressure, prehypertension, and hypertension. From a review of multiple studies, it appears that, for children and adolescents, the largest decline in blood pressure seen with aerobic activity occurs in studies of patients with hypertension.

The results of these epidemiologic studies and clinical trials have led to consideration of using increased physical activity as a therapeutic approach to lower elevated blood pressure. However, since these relationships were not limited to individuals with hypertension, it has also been suggested that increased physical activity can be used as an approach to prevent the development of hypertension. This approach might be particularly helpful in individuals with prehypertension (Lurbe et al. 2009).

Studies also have combined exercise and diet interventions. Some of the studies focused on diet and activity have been designed to prevent obesity

but have also been shown to have a beneficial effect on systolic and diastolic blood pressure (Strong et al. 2005). For example, an 18-month school based multicomponent obesity prevention intervention showed a decrease in the prevalence of hypertension from 17.1% at baseline to 12.8% at 6 months and 15% at 18 months (Kim et al. 2014). Of interest is that increased physical activity has been shown to lower blood pressure in adults (Whelton et al. 2002; Cornelissen and Fagard 2005) and children (Lurbe et al. 2009) independent of any impact on lowering weight or BMI.

From a clinical perspective, it is useful to take a detailed history of physical activity and inactivity as part of the assessment of patients with elevated blood pressure. This assessment may help the clinician understand potential contributors to the development of blood pressure elevation and may also suggest nonpharmacologic approaches via counseling on lifestyle modifications to lower elevated blood pressure.

While different regimens have been used to increase aerobic activity, the most common protocols use approximately 120 min of moderate-intensity exercise a week. Moderate-intensity activity includes brisk walking, where vigorous activity includes running and cycling. Some data suggest that it is easier to sustain moderate levels of activity over longer periods of time and that fewer injuries occur with moderate compared to vigorous physical activity. Current recommendations for adults include increased physical activity in the nonpharmacologic regimen for treating hypertension (Pescatello et al. 2004). The American College of Sports Medicine concluded that the optimal frequency, intensity, time, and type of physical activity need to be better defined, but they recommended that adults with hypertension perform moderate-intensity activity (40–60%  $\dot{V}O_2$  max) for greater than 30 min per day on most, preferably all, days of the week. They suggested that aerobic physical activity should be the primary form but that this could be supplemented by resistance activity (Pescatello et al. 2004).

The mechanisms by which physical activity reduces blood pressure are not completely

understood (Marcus et al. 2006). Possible mechanisms include changes in neurohumoral, vascular, and cardiac structural and functional features. Catecholamine concentrations and insulin resistance decrease in response to chronic exercise; peripheral vascular resistance decreases in response to both acute and chronic endurance physical activity.

There have been far fewer studies of physical activity interventions and blood pressure in children and adolescents. A meta-analysis of 12 randomized clinical trials in children and adolescents showed that overall increased physical activity leads to a small and statistically insignificant reduction in blood pressure (Cai et al. 2014). Strong et al. reviewed the literature related to physical activity and cardiovascular risk factors in youth and found individual studies that demonstrated statistically significant effects of physical activity on lowering blood pressure, particularly in children and adolescents with elevated blood pressure (Lurbe et al. 2009). For example, Danforth et al. used a walking/jogging program in a group of 12 African-American children with hypertension (Danforth et al. 1990). The exercise sessions were for 30 min, 3 days per week for 3 months, with a target intensity of 60–80% of maximum heart rate. They found a 9 mmHg reduction in both systolic and diastolic blood pressure over the course of the program. They also followed the participants after the program was over. There was an ongoing effect for lower systolic blood pressure after detraining. The decrease in blood pressure was independent of decreases in body weight. Hansen et al. studied 68 normotensive and 69 hypertensive children age 9–11 years (Hansen et al. 1991). In this school-based study, the intervention included three additional 50-min sessions of physical education class per week. In hypertensive boys, the systolic blood pressure was reduced on average by 6 mmHg over an 8 month intervention period, but there was no reduction of blood pressure in the girls with hypertension.

No studies have shown a deleterious effect on either aerobic or resistance exercise protocols, especially when they are performed under supervision. These results have led to the recommendations from the National Heart, Lung and Blood Institute that pediatric patients with

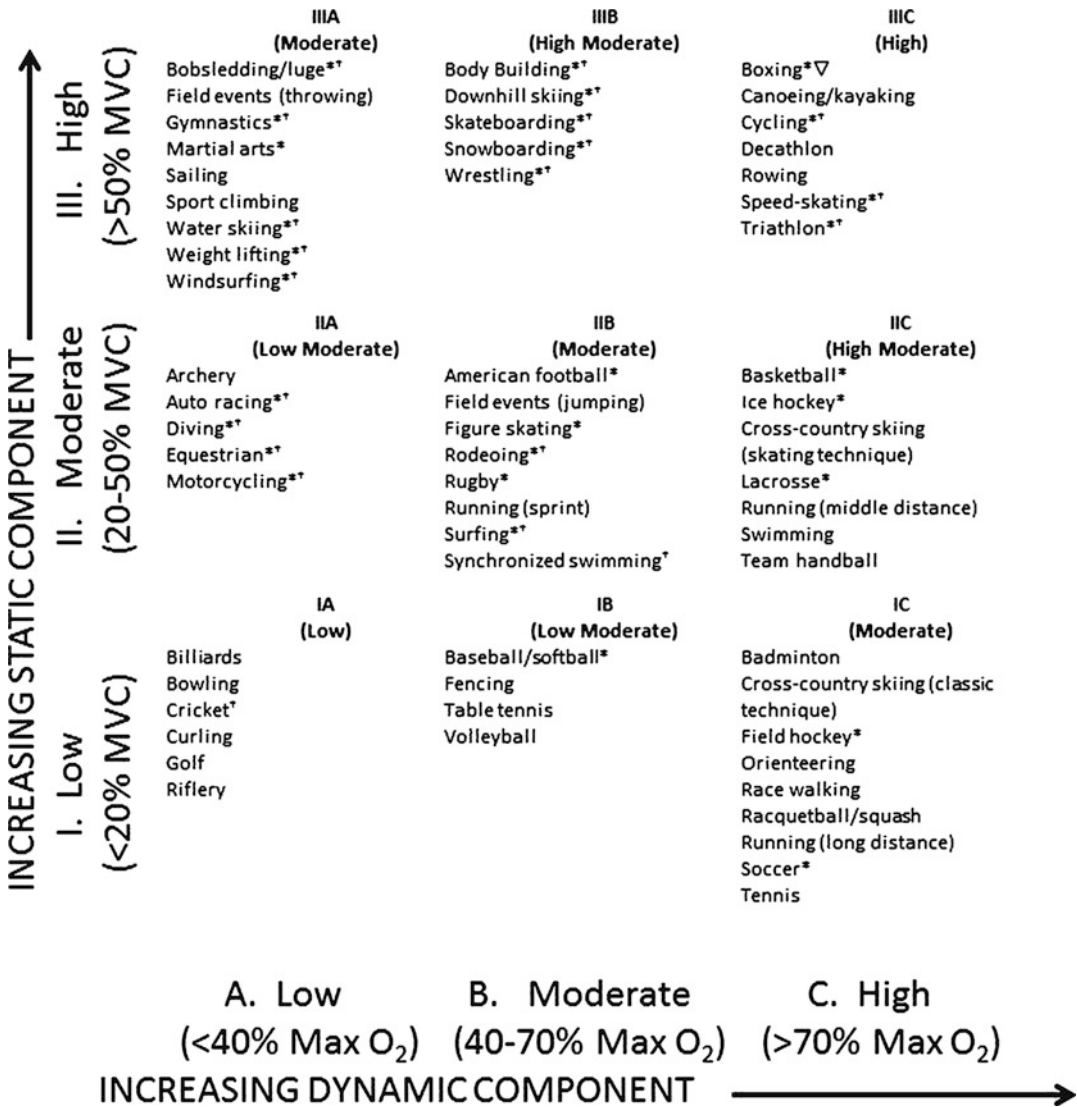
hypertension engage in a lifestyle program including increased physical activity (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents 2011). The recommendation is that children with hypertension should engage in moderate-to-vigorous physical activity on a regular basis. Health care professionals should prescribe moderate-to-vigorous activity for 60 min per day. This regimen should include vigorous intensity (running, playing soccer) activity 3 days per week.

A frequent clinical concern is whether it is safe for children and adolescents with hypertension to participate in athletics. The American Academy of Pediatrics (AAP) has addressed these issues in a policy statement published in 2010 (McCambridge et al. 2010). They recommend that children and adolescents with hypertension should be encouraged to participate in noncompetitive physical activity on a regular basis. However, those children and adolescents who have stage 2 hypertension should be restricted from strenuous physical activity until normal blood pressure is achieved. This is especially true for high static sports (classes 111A-111C Fig. 1). Prehypertension or stage 1 hypertension in the absence of end organ damage, such as left ventricular hypertrophy, should not limit a child's eligibility for competitive sports. These guidelines have been incorporated into the new AAP pediatric hypertension guideline (Flynn et al. 2017).

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## Weight Reduction

One of the most effective ways to manage high blood pressure in children is through weight reduction (Flynn 2012). More than 30% of children in the USA are overweight or obese (Ogden et al. 2012), which represents a large segment of the population with a modifiable risk factor for hypertension. Indeed, a number of observation and population studies have shown a positive association between excess adiposity and high blood pressure in children. Tu et al. (2011) found that systolic blood pressure increased at least four-fold for all races and genders in children that achieved a BMI >85th percentile compared to their normal-weight peers. When analyzed



**Fig. 1** Athletic participation by children and adolescents who have systemic hypertension (Rebecca A. Demorest, Reginald L. Washington, Council on Sports Medicine and Fitness. *Pediatrics* Jun 2010, 125 (6) 1287–1294; DOI:

10.1542/peds.2010-0658. Reproduced with permission from *Pediatrics*. Vol 125(6). Pages 1287–1294. Copyright © 2010 by the American Academy of Pediatrics)

further, each 5% increase in BMI percentile for overweight children nearly doubled their risk of hypertension or prehypertension. For overweight black females, the risk increased by 33%. In a cross-sectional study, Nelson et al. (2015) analyzed the effects of excess adiposity in children on risk factors of CVD using data from the Poudre Valley Health System, Healthy Hearts Club of Colorado. In the 9,694 children analyzed,

researchers found that every risk factor for CVD was significantly higher in overweight and obese children relative to children of a normal weight. Notably, systolic blood pressure and diastolic blood pressure were 8% higher in obese compared to normal weight children.

Beyond elevated blood pressure, excess adiposity in childhood has been linked to adverse cardiovascular sequelae including left ventricular

hypertrophy (LVH) and increased carotid intima-media thickness (IMT), both of which have been linked with adverse cardiovascular events in adulthood (Nadeau et al. 2011). Using data from the Bogalusa Heart Study, Freedman et al. (2008) analyzed the relationship between BMI and adult carotid IMT. On average, BMI and cardiovascular measurements were taken seven times for each participant, first as children and later as adults. Researchers found that levels of IMT as an adult were correlated with the first childhood BMI measurement, as well as collective BMI measurements taken throughout childhood (Freedman et al. 2008). In a cross-sectional study of 141 hypertensive children between the ages of 3 and 20 years, Pruetto et al. (2013) found that BMI z-score was a significant predictor of LVH even after adjustment for relevant confounders. Taken together, these studies underscore the importance of weight control in long term cardiovascular health.

Lifestyle interventions that achieve weight loss have consistently shown a favorable impact on blood pressure and other cardio-metabolic risk factors (Ho et al. 2012). Kirk et al. demonstrated that, in the context of a clinical weight management program involving diet, exercise and behavior modification, improvement in BMI was associated with improvement in systolic blood pressure, as well as other CVD risk factors (Kirk et al. 2005). Recently, Reinehr et al. (2016) prospectively analyzed results from a 1-year weight loss intervention in overweight and obese children between the ages of 5 and 17 years. Participants who were able to reduce their BMI standard deviation score (SDS) by  $\geq 0.25$  in 1 year (equivalent to a BMI reduction of 0.5 kg/m<sup>2</sup> in a 7-year-old child and 1.0 kg/m<sup>2</sup> in a 13-year-old) achieved an average reduction in systolic blood pressure and diastolic blood pressure of -3.2 mmHg and -2.2 mmHg, respectively. Furthermore, a BMI-SDS reduction of about  $>0.5$  more than doubled the blood pressure response, with -6.0 mmHg and -5.1 mmHg reductions in systolic and diastolic blood pressure, respectively. In general, dietary intervention studies that produce weight loss in youth consistently show favorable effects on blood pressure (National High Blood

Pressure Education Program 2004; Flynn 2012). The challenge is in designing weight management programs that have good retention rates and sustained weight loss or maintenance over time.

An evidenced-based, best practices model regarding pediatric weight management has been published (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents 2011; Barlow 2007). This includes a strong focus on behavior change related to improving diet and increasing the level of physical activity. The behavior change principles of stimulus control, goal setting, recording of diet and activity (self-monitoring), and rewards have been empirically shown to promote favorable eating behavior change (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents 2011). Stimulus control includes changing the environment to reduce availability of calorie-dense food to encourage physical activity while discouraging sedentary time. Elimination of television or computers from a child's bedroom is an example of stimulus control. Parents should work with their children to set goals that can be accomplished and monitored. For example, because skipping meals is associated with increased BMI, eating breakfast at least 5 days each week would be such a goal. Once a goal is set, it is important to monitor progress toward the goal. This can happen in a variety of ways, but a simple chart of daily eating and activity can work quite well. The reward should be meaningful but small. Food should never be used as a reward in any setting, including at school. The reward should be tailored to the age and developmental stage and interests of the child.

Motivational interviewing has been suggested as an approach to better understand how patients and their family understand the changes to be made and helps the clinician understand the perceived barriers to change (Resnow and McMaster 2012). Instead of a prescriptive approach, motivational interviewing involves an interaction between the provider and the patient. It often involves a negotiation around what the patient believes is important and what they think can be accomplished. This approach is helpful in

building small, incremental, but sustainable changes in behavior. Creating a home food environment that provides positive encouragement and role modeling, family meals together, parenting rules around eating, and availability and access to healthy foods are factors conducive to promoting healthy weight status and high diet quality in children (Couch et al. 2014).

## Other Nonpharmacological Approaches

Some other approaches to treatment of high blood pressure, often referred to as alternative or complementary interventions, have been evaluated. For example, Breathing Awareness Meditation, which is a component of mindfulness, was shown to reduce daytime, nighttime, and 24-h systolic blood pressure and diastolic blood pressure in normotensive and prehypertensive African-American adolescents (Kabat-Zinn and Hanh 1991). Participation in Hatha Yoga resulted in improvement of blood pressure in a small ( $n = 4$ ) group of children with prehypertension (Sieverdes et al. 2014). Other interventions, such as transcendental meditation, have not been shown to lower blood pressure in adolescents (Barnes et al. 2012). At present, it is not recommended that these alternative relaxation and stress reduction approaches be utilized in the standard clinical approach to children with hypertension. Nevertheless, further research in this area is warranted.

## Conclusions

Nonpharmacologic treatment is important in the management of prehypertension and hypertension in youth. Several interventions, including those focused on sodium reduction, a DASH dietary pattern, and increasing physical activity, now present true evidence-based approaches to management. However, questions remain on many aspects of lifestyle approaches to managing hypertension in children and adolescents. For example, studies are needed to address whether there may be some patients who respond better to some dietary

changes than others. Further, what is the best regimen of physical activity, including type, intensity, duration, and frequency of physical activity for blood pressure management? How should lifestyle changes be used to complement pharmacologic treatment when that is necessary? What is the best way to achieve and monitor behavioral change? Answers to these questions will be quite important to refine nonpharmacologic therapy for hypertension in children and adolescents in the future.

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# Pharmacologic Treatment of Pediatric Hypertension

# 44

Michael A. Ferguson

## Abstract

Hypertension has traditionally been regarded as a rare occurrence in childhood and adolescence; however, there is compelling evidence to suggest that elevated blood pressure is increasingly common in this population, particularly in those with obesity. As a result, pediatricians increasingly are expected to evaluate and manage patients with elevated blood pressure. An increased emphasis on conducting drug trials in children over the last two decades has yielded important advances with respect to evidence-based data regarding the safety and efficacy of antihypertensive medications in children and adolescents. Despite these advances, data to definitively guide selection of first-line antihypertensive agents is lacking. This chapter provides an overview of antihypertensive drug therapy in children, including indications for treatment. A detailed review of available antihypertensive agents is provided with an emphasis on pediatric specific data with respect to dosing, safety, and efficacy. In addition, a rational approach to selecting an appropriate

medication with respect to pathophysiology, putative benefit, and likelihood for side effects is reviewed.

## Keywords

Pharmacotherapy • Clinical trials • ACE inhibitors • Angiotensin receptor blockers • Calcium channel blockers • Beta-adrenergic blockers • Vasodilators • Diuretics

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The original version of this chapter was revised: The maximum dose for Captopril in Table 3 was incorrectly listed as 0.6 mg/kg/day. A correction to this chapter can be found at [https://doi.org/10.1007/978-3-319-31107-4\\_56](https://doi.org/10.1007/978-3-319-31107-4_56)

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## Introduction

Historically, hypertension was thought to be exceedingly rare in young children and uncommon in adolescents. As recently as the early 1970s, there was ongoing debate regarding the clinical utility of routine blood pressure (BP) screening in the general pediatric population (Gordon 1973; Loggie 1973). In addition, there was no widely accepted definition of what constituted a hypertensive BP reading in children. Established standards for normal BP in infants and children of varying ages existed (Londe 1968; Moss and Adams 1962); however, in practice, BP values exceeding 130–140/85–90 were arbitrarily considered to be the upper limits of normal in all children. Results from the first Health and Nutrition Examination Survey (1971–1974) suggested that pediatric hypertension was far more common than previously thought (Roberts and Maurer 1977). Although they reported a prevalence rate of only 0.8% in 12–17-year-olds, the definition used for hypertension was systolic BP > 160 mmHg or diastolic BP > 95 mmHg. When a less restrictive definition was applied (systolic BP > 140 or diastolic BP > 90), the prevalence rate in the same age group increased to 5.6% (Roberts and Maurer 1977). Around this time, pharmacologic treatment of childhood hypertension was generally restricted to those with an established underlying cause and/or symptomatic disease. Given the rarity with which antihypertensive drugs were used in children, it is not surprising that young patients were largely ignored in early studies evaluating the safety and efficacy of these agents.

Over the last four decades, childhood BP has been studied more rigorously, resulting in clearer definitions of pediatric BP values and consensus recommendations pertaining to appropriate BP measurement and monitoring. This has resulted in a broader understanding of the prevalence of childhood hypertension as well as the implications of hypertension for overall short-term and long-term

health. In addition, indications for the initiation of drug therapy have been further clarified. Since the National Heart, Lung, and Blood Institute (NHLBI) commissioned the First Task Force on Blood Pressure Control in Children in 1977, normative BP values have been adopted as the standard for assessment of BP in children (Blumenthal et al. 1977). Hypertension has been defined as BP consistently above the 95th percentile for age, gender, and height. Normative BP values have been refined over time, with the most recent update published in the 2017 American Academy of Pediatrics pediatric hypertension guideline (Flynn et al. 2017). Table 1 summarizes the current BP classification scheme from that document.

The widespread adoption of these definitions has facilitated increased uniformity in the classification of pediatric BP. As a result, the scope of disease burden has come into sharper focus. Screening studies dating back to the late 1970s and 1980s estimated that less than 2% of children were persistently hypertensive (Sinaiko et al. 1989; Fixler et al. 1979). These studies also demonstrated the necessity of repeated BP measurement in order to make an accurate diagnosis of hypertension, as there is a clear trend of regression toward the mean in those with initially elevated readings, as well as significant lability of BP values, even in children with secondary forms of hypertension. Disturbingly, several recent studies suggest that the percentage of children and

**Table 1** Classification of blood pressure in children

Blood pressure classification	Blood pressure percentiles
Normal	SBP and DBP < 90th percentile
Elevated blood pressure	SBP or DBP ≥ 90th percentile and <95th percentile; or 120–129/<80 mmHg for adolescents ≥13 years old
Stage 1 hypertension	SBP or DBP >95th percentile up to the 95th percentile+11 mmHg; or 130–139/80–89 mmHg for adolescents ≥13 years old
Stage 2 hypertension	SBP or DBP ≥95th percentile+12 mmHg; or >140/90 mmHg for adolescents ≥13 years old

BP blood pressure, DBP diastolic blood pressure, SBP systolic blood pressure

adolescents with hypertensive BP readings has doubled in the last two decades, with 3–5% now affected (Sorof et al. 2004; McNiece et al. 2007; Din-Dzietham et al. 2007). In addition, there has been a concomitant rise in the prevalence of prehypertension, with 10–15% of youths now affected (Din-Dzietham et al. 2007; McNiece et al. 2007), as well as an increase in absolute systolic and diastolic BP values of 1.4 and 3.3 mmHg, respectively (Muntner et al. 2004). This upward trend in BP has generally been attributed to the ongoing childhood obesity epidemic.

With these data in mind, it is reasonable to assert that childhood hypertension can no longer be considered a rare entity. Pediatric providers are confronted with patients with elevated BP with increasing regularity. Unfortunately, there is some evidence that primary care pediatricians remain uncomfortable with the evaluation and treatment of children with elevated BP (Boneparth and Flynn 2009; Yoon et al. 2012). With respect to pharmacologic therapy, this is understandable given the underrepresentation of pediatric patients in drug trials and the attendant lack of clear dosing guidelines for the pediatric population historically. Fortunately, legislative efforts over the last two decades have led to substantive improvements in this area. The Food and Drug Administration Modernization Act (FDAMA) in 1997 included financial incentives to drug manufacturers for conducting studies in children. Specifically, Section 505A, known as the Pediatric Exclusivity Provision, provided an additional 6-month patent extension, or marketing exclusivity, to manufacturers for completing trials designed to provide necessary pediatric efficacy, safety, and dosing information to physicians in product labeling (USFDA 1997). Successor legislation, including the Best Pharmaceuticals for Children Act (BPCA) in 2002 and Pediatric Research Equity Act (PREA) in 2003, not only extended the financial incentives outlined above but also required manufacturers to conduct studies to provide adequate labeling if a drug is likely to be used by a substantial number of pediatric patients or if there is reason to believe that a drug would represent a meaningful therapeutic benefit over existing therapies (USFDA 2002, 2003b). Most recently, the Food and Drug Administration Safety and Innovation Act (FDASIA) (USFDA

2004), passed in 2012, permanently reauthorized BPCA and PREA, tightened up some of the provisions of PREA, and extended the mandate of BPCA to include neonates.

These legislative efforts have thus far proven quite effective, stimulating a marked increase in the number of pharmaceutical studies in children. Cardiovascular medications, including antihypertensive agents, have been one of the largest categories impacted. As mandated by FDAMA, the FDA developed a “Pediatric Priority List” of drugs for which additional pediatric information may produce health benefits in the pediatric population. The initial list, published in 1998, included 492 medications, over 50 of which were oral antihypertensive agents (Pasquali et al. 2002). To date, the FDA has issued a written request to pharmaceutical companies for pediatric studies of 424 approved active moieties under the Pediatric Exclusivity Provision (USFDA 2016c). As of September 2016, a total of 217 drugs had been granted exclusivity, 18 of which are antihypertensive medications (Table 2; USFDA 2016b).

**Table 2** FDAMA-related antihypertensive medication studies and exclusivity status (as of April 2014)

Drug	Exclusivity granted	Pediatric labeling
Amlodipine	11/27/2001	Yes
Benazepril	7/2/2003	Yes
Betaxolol <sup>a</sup>	2/28/2007	
Bisoprolol/HCTZ	4/19/2000	No
Candesartan	7/20/2009	Yes
Carvedilol <sup>a</sup>	11/8/2006	
Enalapril	2/2/2000	Yes
Eplerenone	10/24/2007	No
Esmolol	8/22/2003	No
Felodipine	8/30/2001	No
Fosinopril	1/27/2003	Yes
Irbesartan	9/26/2004	Yes
Lisinopril	11/19/2001	Yes
Losartan	3/20/2002	Yes
Metoprolol	7/27/2006	Yes
Quinapril	6/7/2002	No
Timolol <sup>a</sup>	2/28/2007	
Valsartan	8/8/2007	Yes

<sup>a</sup>Antihypertensive agents that have been granted exclusivity for indications other than hypertension

All of the completed antihypertensive medication trials have followed one of four FDA-approved study designs to assess efficacy and dose response (Pasquali et al. 2002). Some studies did not demonstrate efficacy, most likely due to inadequate dose selection and other design issues (Benjamin et al. 2008). Additionally, earlier studies were relatively short in duration, making it difficult to draw meaningful conclusions about drug safety. Fortunately, more recent trials have incorporated an open-label extension period, typically lasting 52 weeks, providing a greater opportunity to assess the adverse effect profile. Although not specifically mandated by FDAMA and related legislation, several of the studies included an extemporaneous drug suspension into the study design. The suspensions used have been incorporated into the FDA-approved prescribing information, allowing for more specific dosing recommendations and ease of administration in younger children.

There is now a growing list of antihypertensive medications approved by the FDA for pediatric use. Similar efforts in Europe, specifically the Regulation of Medicinal Products for Paediatric Use, promise to further promote the rigorous study of antihypertensive medications in children (Lurbe et al. 2009) moving forward. Therefore, pediatric providers should feel emboldened by the increasing body of evidence-based data with respect to dosing, efficacy, and safety of antihypertensive drugs in children. It should, however, be noted that data pertaining to long-term outcomes of children receiving antihypertensive drug therapy, including effects on target-organ damage, cardiovascular morbidity, and neurodevelopmental outcome, remain limited.

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## General Approach to the Hypertensive Child

The 2017 pediatric hypertension guidelines issued by the American Academy of Pediatrics (AAP) (Flynn et al. 2017) provide clinicians with updated recommendations for BP screening in the pediatric population as well as guidelines for

the diagnosis, evaluation, and treatment of hypertension. Revised tables are provided that include the 50th, 90th, and 95th percentiles by gender, age, and height as well as a revised classification scheme that aligns with updated adult hypertension guidelines. Based on these guidelines, annual BP screening is presently recommended in all children  $\geq 3$  years of age; routine BP measurement in children  $< 3$  years is limited to those with increased risk of hypertension (Flynn et al. 2017).

If BP elevations are noted on screening, confirmation using appropriate equipment and measurement technique is critical. Given the high prevalence of reactive (“white coat”) hypertension in children (Hornsby et al. 1991; Swartz et al. 2008; Sorof and Portman 2000), ambulatory BP monitoring (ABPM) should be obtained to confirm elevated office readings (see ► Chap. 16, “Ambulatory Blood Pressure Monitoring Methodology and Norms in Children”). In those with confirmed hypertension, a detailed evaluation is recommended to distinguish between primary and secondary hypertension, to assess for additional cardiovascular risk and to assess for target end-organ damage (see ► Chaps. 38, “Diagnostic Evaluation of Pediatric Hypertension” and ► 39, “Sequelae of Hypertension in Children and Adolescents”). In all patients, appropriate counseling regarding therapeutic lifestyle changes is indicated. Recommendations in this regard generally involve family based-interventions to modify the diet, increase physical activity, and facilitate weight loss when appropriate (see ► Chap. 43, “Nonpharmacologic Treatment of Pediatric Hypertension”). In childhood, drug therapy for hypertension is typically reserved for patients who have failed non-pharmacologic therapy, those with symptomatic hypertension, and those with stage 2 hypertension (Flynn et al. 2017).

In the adult population, death from ischemic heart disease and stroke increases progressively and linearly from systolic and diastolic BPs of 115 and 75 mmHg, respectively (Lewington et al. 2002). Efforts to increase awareness of the risks associated with hypertension and optimize

therapy in adults have resulted in favorable trends in morbidity and mortality attributed to hypertension (Chobanian et al. 2003). Cardiovascular events are rare in children and, therefore, are not practical endpoints in the study of antihypertensive therapies. Although subclinical target end-organ damage (left ventricular hypertrophy, increased carotid artery intimal-medial thickness; discussed in detail in ► Chap. 38, “Diagnostic Evaluation of Pediatric Hypertension”) (Daniels et al. 1998; Sorof et al. 2003; Hanevold et al. 2004) has been increasingly recognized in hypertensive children, there are few studies looking at the impact of therapy on progression and/or regression. Given the paucity of outcome-based studies in the pediatric population, goals for antihypertensive therapy in children have not been well established and are largely inferred from adult studies. As recommended in the 2017 AAP guideline, the BP goal for all children is reduction of BP <90th percentile, or <130/80 in teens  $\geq 13$  years of age (Flynn et al. 2017). Recent recommendations by the European Society of Hypertension similarly target BPs below the 90th percentile in uncomplicated hypertensive children, below the 75th percentile in children with CKD, and below the 50th percentile in children with concomitant CKD and proteinuria (Lurbe et al. 2009). These targets were derived based on evidence that more aggressive BP control may be particularly beneficial in slowing renal functional decline in children with chronic kidney disease (Wuhl et al. 2009). It should be noted that the CKD goals in the European guidelines refer to percentiles based on mean arterial pressure (MAP) on ABPM and that equivalent targets for office based BP measurement are currently unknown.

When antihypertensive drug therapy is necessary, a stepped-care approach to the initiation and escalation of drug dosing is typically recommended (Flynn and Daniels 2006; NHBPEP 2004). After a first-line agent is selected, it should be started at the lowest recommended dose with ongoing BP monitoring to determine effect. If the BP remains above the desired range, the dose is gradually increased until adequate BP control is achieved or until the maximum recommended dose is reached,

at which time a medication from a different class should be added. All patients require monitoring for medication-related side effects, which may be dose limiting and require addition of a second agent earlier than expected (prior to reaching the maximum dose of the first agent), or may require replacement of the first agent altogether.

Studies directly comparing the efficacy of the different classes of antihypertensive medications in children are lacking. One notable exception is the randomized, double-blind, parallel group study completed by Schaefer et al. that reported comparable BP reductions and adverse events in hypertensive children treated with enalapril or valsartan (Schaefer et al. 2011). Other studies evaluating the BP-lowering effect of the various antihypertensive classes in children have demonstrated a significant absolute reduction in BP as a result of treatment (Blowey 2012), with angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARBs), and calcium channel blockers (CCB) demonstrating similar antihypertensive efficacy (Simonetti et al. 2007). Although specific drugs may be preferential in individual clinical settings based on putative benefits, predicted response, or potential adverse effects, considerable variation exists in the choice of a first agent. For example, a survey of pediatric nephrologists revealed that 47% used ACE inhibitors, 37% CCBs, 15.3% diuretics, and 6.6% beta-adrenergic blockers as first-line therapies in primary hypertension (Woroniecki and Flynn 2005). With this in mind, considerable uncertainty still exists as to whether an “ideal” first-line agent for hypertensive children can be identified (Batisky 2012). In an effort to provide comparative effectiveness data on therapeutic options for the treatment of older children with primary hypertension, Samuel et al. have designed a series of n-of-1 randomized trials to identify preferred single drug therapy from among ACE inhibitors, CCBs, and diuretics (Samuel et al. 2016). The study opened to recruitment in June 2013, though it remains unclear when the results will be published.

The following sections provide a review of classes of antihypertensive agents, emphasizing



those with existing pediatric efficacy and safety data. For each class, a brief summary of the mechanism of action is provided. Table 3 provides dosing guidelines for medications commonly used in hypertensive children.

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## Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors have a number of modulatory effects on the renin-angiotensin-aldosterone system that result in a reduction in BP. Foremost, ACE inhibitors downregulate the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor that also stimulates the secretion of aldosterone from the adrenal cortex. In addition, ACE inhibitors prevent the metabolism of bradykinin, an endogenous vasodilator and stimulator of natriuresis through direct renal tubular effects (Brown and Vaughan 1998).

Relative to other antihypertensive classes, ACE inhibitors have the largest body of evidence supporting their use in pediatric patients (Meyers and Siu 2011). Nearly all of these agents have been systematically studied in FDAMA-related industry-sponsored trials. As a result, there are pediatric specific data related to dosing, efficacy, and safety. One notable exception is captopril, the first orally available ACE inhibitor. Captopril was developed in 1975 and received FDA approval for the treatment of adult hypertension in 1981 (DiBianco 1985; Smith and Vane 2003). In 1979, Oberfield et al. (1979) described the use of captopril in the successful treatment of a child with malignant hypertension refractory to therapy with other oral antihypertensive agents. Since that time, a number of small, uncontrolled, and largely descriptive studies have recapitulated the utility of captopril in hypertensive children over a broad range of age groups and helped elucidate complications associated with therapy, including hypotension, hyperkalemia, diminished glomerular filtration rate (GFR), and leukopenia (Mirkin and Newman 1985; Sinaiko et al. 1983, 1986; Tack and Perlman 1988). Although captopril does not have a pediatric

specific indication, owing largely to its patent expiration prior to passage of the FDAMA, established dosing guidelines exist (NHBPEP 2004), and it continues to be a valuable agent in the treatment of selected children with elevated BP. Information is available for the preparation of a stable extemporaneous solution.

Well-designed pediatric specific trials have been conducted for most of the longer-acting ACE inhibitors, resulting in published safety and efficacy data. Enalapril, lisinopril, and fosinopril have been studied using similar double-blind, placebo controlled, dose-response designs. In patients aged 6–16 years, enalapril and lisinopril were both found to reduce BP in a dose-dependent manner that was maintained across all study subgroups (age, gender, race, and ethnicity) (Wells et al. 2002; Soffer et al. 2003). Minimum effective doses were similar for enalapril and lisinopril (0.08 and 0.07 mg/kg/day, respectively). Few adverse events were reported during either trial; however, the short duration of each (4 weeks) precluded robust conclusions with respect to safety and tolerability. In a more recent trial, the pharmacokinetics, pharmacodynamics, and safety of lisinopril were evaluated in pediatric kidney transplant recipients (Trachtman et al. 2015). Lisinopril was found to be effective and well tolerated with similar pharmacokinetics to use in those without a kidney transplant. FDA-approved labeling for enalapril and lisinopril includes clear dosing guidelines as well as instructions for preparation of an extemporaneous suspension (USFDA 2016a). In addition, both enalapril and lisinopril are now available as commercially prepared oral solutions.

The fosinopril trial demonstrated substantial reduction of systolic and diastolic BP in low (0.1 mg/kg/day)-, medium (0.3 mg/kg/day)-, and high (0.6 mg/kg/day)-dose groups; however, no-dose response relationship was observed (Li et al. 2004). During the randomized placebo withdrawal phase, a significant increase in systolic BP was observed in the placebo arm, though the absolute difference between the two groups was only 3.7 mmHg. The study included a 52-week open-label extension, during which BP

**Table 3** Medications for the treatment of hypertension in children

Class	Drug	Starting dose	Interval	Maximum dose <sup>a</sup>
ARAs	Eplerenone	25 mg/day	QD – BID	100 mg/day
	Spirolonolactone <sup>b</sup>	1 mg/kg/day	QD – BID	3.3 mg/kg/day up to 100 mg/day
	Candesartan <sup>b</sup>	1–6 years: 0.2 mg/kg/day; 6–17 years: <50 kg 4–8 mg QD >50 kg 8–16 mg QD	QD	1–6 years: 0.4 mg/kg/day; 6–17 years: <50 kg 16 mg daily >50 kg 32 mg daily
ARBs	Losartan <sup>b</sup>	0.75 mg/kg/day (up to 50 mg QD)	QD	1.4 mg/kg/day (max 100 mg QD)
	Olmesartan <sup>b</sup>	20–35 kg: 10 mg QD ≥35 kg: 20 mg QD	QD	20–35 kg: 20 mg QD ≥35 kg: 40 mg QD
	Valsartan <sup>b</sup>	<6 years: 5–10 mg/day 6–17 years: 1.3 mg/kg/day (up to 40 mg QD)	QD	<6 years: 80 mg QD 6–17 years: 2.7 mg/kg/day (up to 160 mg QD)
ACE inhibitors	Benazepril <sup>b</sup>	0.2 mg/kg/day (up to 10 mg/day)	QD	0.6 mg/kg/day (up to 40 mg/day)
	Captopril <sup>b</sup>	0.3–0.5 mg/kg/dose	BID – TID	6 mg/kg/day (up to 450 mg/day)
	Enalapril <sup>bc</sup>	0.08 mg/kg/day	QD – BID	0.6 mg/kg/day (up to 40 mg/day)
	Fosinopril	0.1 mg/kg/day (up to 10 mg/day)	QD	0.6 mg/kg/day (up to 40 mg/day)
	Lisinopril <sup>bc</sup>	0.07 mg/kg/day (up to 5 mg/day)	QD	0.6 mg/kg/day (up to 40 mg/day)
	Quinapril	5–10 mg/day	QD	80 mg/day
	Carvedilol <sup>b</sup>	0.1 mg/kg/dose (up to 6.25 mg BID)	BID	0.5 mg/kg/dose up to 25 mg BID
β-adrenergic antagonists	Labetalol <sup>b</sup>	2–3 mg/kg/day	BID	10–12 mg/kg/day (up to 1.2 g/day)
	Atenolol <sup>b</sup>	0.5–1 mg/kg/day	QD	2 mg/kg/day up to 100 mg/day
	Bisoprolol/HCTZ	2.5/6.25 mg daily	QD	10/6.25 mg daily
	Metoprolol	1–2 mg/kg/day	BID	6 mg/kg/day (up to 200 mg/day)
	Propranolol <sup>c</sup>	1 mg/kg/day	BID – QID	8 mg/kg/day (up to 640 mg/day)
	Amlodipine <sup>b</sup>	0.06 mg/kg/day	QD	0.3 mg/kg/day (up to 10 mg/day)
	Felodipine	2.5 mg/day	QD	10 mg/day
CCBs	Isradipine <sup>b</sup>	0.05–0.15 mg/kg/dose	TID – QID	0.8 mg/kg/day up to 20 mg/day
	Extended-release nifedipine	0.25–0.5 mg/kg/day	QD – BID	3 mg/kg/day (up to 120 mg/day)

(continued)

**Table 3** (continued)

Class	Drug	Starting dose	Interval	Maximum dose <sup>a</sup>
Central $\alpha$ -agonist	Clonidine <sup>b</sup>	5–20 mcg/kg/day	QD – BID	25 mcg/kg/day (up to 0.9 mg/day)
Diuretics	Amiloride	5–10 mg/day	QD	20 mg/day
	Chlorthalidone	0.3 mg/kg/day	QD	2 mg/kg/day (up to 50 mg/day)
	Furosemide <sup>c</sup>	0.5–2 mg/kg/dose	QD – BID	6 mg/kg/day
	HCTZ	0.5–1 mg/kg/day	QD	3 mg/kg/day (up to 50 mg/day)
Vasodilators	Hydralazine	0.25 mg/kg/dose	TID – QID	7.5 mg/kg/day (up to 200 mg/day)
	Minoxidil	0.1–0.2 mg/kg/day	BID – TID	1 mg/kg/day (up to 50 mg/day)

*HCTZ* hydrochlorothiazide

<sup>a</sup>The maximum recommended adult dose should not be exceeded

<sup>b</sup>Information on preparation of a stable extemporaneous suspension is available for these agents

<sup>c</sup>Available as a FDA approved commercially supplied oral solution

reduction was maintained long term on fosinopril with favorable safety and tolerability profiles. Unfortunately, fosinopril was administered only in the tablet form during the study. As a result, the FDA-approved label information only includes dosing recommendations for children weighing >50 kg, as an appropriate dose strength is not available for those weighing <50 kg (USFDA 2016a). Of note, post hoc analysis of the fosinopril trial results demonstrated reduced efficacy in black children compared to nonblack children, a finding similar to studies of ACE inhibitors in adults (Menon et al. 2006; Brewster et al. 2004).

There are limited published data regarding the efficacy and safety of benazepril, quinapril, and ramipril. FDA analyses of the benazepril and ramipril trials are, however, available online. Benazepril was granted pediatric exclusivity after pharmacokinetic (PK), and dose-response studies were submitted to the FDA (USFDA 2003a). Dose-response analysis demonstrated positive slopes for both systolic and diastolic BP though did not reach statistical significance (USFDA 2003a). The placebo group exhibited a significant withdrawal effect, with increases in mean systolic (5.18 mmHg) and diastolic (5.16 mmHg) BP greater than the mean changes in the overall benazepril group. PK studies also found an extemporaneously compounded suspension to be bioequivalent to the tablet formulation. Thus, FDA-approved labeling for benazepril includes pediatric specific dosing recommendations as well as instructions for preparation of the suspension. Results from the ramipril trial were disappointing. Specifically, prospective analyses of BP showed no significant effects (USFDA 2006). The only pediatric data published regarding quinapril are from a small PK study in 24 patients aged 2.5 months to 6 years. Effect of therapy on BP was not reported and dosing guidelines for children are not available.

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## Angiotensin Receptor Blockers

ARBs, like ACE inhibitors, produce a BP-lowering effect through modulation of the renin-angiotensin-aldosterone system. Specifically, ARBs act by selectively inhibiting the

activation of the angiotensin II type I receptor by angiotensin II, thereby blocking the pathways that lead to vasoconstriction and water retention (Ram 2008). In so doing, angiotensin II is diverted to the angiotensin II type II receptor, which, among other actions, mediates vasodilation and decreases tubular sodium reabsorption (Ram 2008).

As one of the newest antihypertensive drug classes, virtually all ARBs were still on patent when the FDAMA was enacted. As a result, industry-sponsored trials have provided a wealth of reliable data regarding dosing, efficacy, and safety of these agents in children and adolescents. Thus far, pediatric exclusivity has been granted for losartan, candesartan, olmesartan, and valsartan (USFDA 2016a), with additional agents of this class still under study in the pediatric age group.

The losartan trial evaluated the effect of once-daily dosing of this agent on hypertensive children 6–16 years of age (Shahinfar et al. 2005). After 3 weeks of therapy, significant dose-dependent reductions of diastolic and systolic BP were demonstrated. During the randomized placebo wash-out phase, BP increased after discontinuation of losartan in moderate-dose (0.75 mg/kg) and high-dose (1.44 mg/kg) groups though no difference was noted in the low-dose (0.07 mg/kg) group, suggesting a similar response to placebo. Based on these results, 0.75 mg/kg/day has been recommended as an effective starting dose. Losartan was well tolerated across all dosing ranges, although the brief study duration (5 weeks) precluded robust conclusions regarding safety. A suspension formulation was studied, and instructions for preparation are provided in the FDA-approved labeling information along with pediatric specific dosing guidelines. A randomized, open-label, dose-response study of losartan was recently completed in younger children (6 months–6 years) (Webb et al. 2014). Subjects were randomized to low (0.1 mg/kg/day), medium (0.3 mg/kg/day), and high (0.7 mg/kg/day) doses. After 3 weeks, a significant systolic and diastolic blood pressure reduction was noted in all three groups; however, no dose-response relationship was noted. A 24-month extension study was completed, during which sustained blood pressure-lowering effect was noted with a low incidence

of adverse events. At this point, it is not clear if the results will lead to an extension of the FDA-approved labeling to this lower age range.

Candesartan has been studied in pediatric patients ranging in age from 1 to 17 years (Trachtman et al. 2008; Schaefer et al. 2010). In older children (6–17 years), no dose-response relationship was demonstrated across low-, moderate-, and high-dose treatment groups; however, systolic BP was noted to be significantly reduced in all treatment groups when compared to placebo (Trachtman et al. 2008). There was no apparent difference in BP response based on age, sex, or Tanner stage, though the reduction in BP did appear to be attenuated in blacks compared to nonblacks. Response appeared to be sustained over a 52-week open-labeled extension phase with safety and tolerability profiles comparable to adults. In younger children (1–6 years), dose-dependent decreases in systolic and diastolic BP were observed that appeared to be independent of age, sex, or race (Schaefer et al. 2010). No placebo-controlled washout phase was included, though a 52-week extension phase did suggest that the antihypertensive effect of candesartan was sustained with good tolerability and safety profiles. A preplanned regression analysis combined the efficacy results from both candesartan trials and demonstrated that reductions in systolic BP and diastolic BP were monotonic and dose related for the 1–17 age range as a whole (Schaefer et al. 2010). FDA-approved labeling includes dosing recommendations for children 1–17 years as well as instructions for the preparation of a stable oral solution (USFDA 2016a).

Similar to candesartan, valsartan trials have been completed in hypertensive children ranging in age from 1 to 16 years. In older children (6–16 years), valsartan therapy resulted in dose-dependent reductions in systolic and diastolic BP that were independent of weight, age, sex, and race (Wells et al. 2002). During the placebo withdrawal phase, the increase in BP was significantly higher in the pooled placebo group compared to the pooled valsartan group. During the 52-week open-label phase, valsartan was well tolerated with rare serious adverse events. In younger children (1–5 years), valsartan treatment significantly

lowered systolic and diastolic BP in low-, medium-, and high-dose groups; however, no dose-response relationship was demonstrated. The BP-lowering effect was further confirmed by reversal of effect in those assigned to placebo during the withdrawal. As with the older cohort of children, a favorable safety and tolerability profile was seen during the 52-week open-label extension phase. Additionally, effects on development were assessed, although in a limited fashion, and showed no adverse effects of valsartan. Dosing ranges for 6–16-year-olds now appear on the FDA-approved labeling as do instructions for preparation of suspension; however, use is not recommended in children less than 6 years of age due to safety concerns (Tullus 2011).

Irbesartan and olmesartan have both been studied in pediatric patients as well. The olmesartan trial in 6–16-year-old children demonstrated a dose-response effect, though only two dosing regimens were evaluated (Hazan et al. 2010). This study included a separate cohort of black children. Although BP-lowering efficacy was observed in patients of all ethnic backgrounds, the predominantly nonblack patient cohort achieved greater BP reductions than the black patient cohort. FDA-approved labeling for olmesartan includes dosing guidelines for children 6–16 years as well as instructions for solution preparation. Early studies of irbesartan suggested efficacy in hypertensive children, particularly those with chronic kidney disease (Sakarcan et al. 2001; Franscini et al. 2002). However, a later study did not find a significant effect on systolic BP at doses ranging from 0.5 to 4.5 mg/kg (USFDA 2004). As a result, the FDA-approved labeling states the irbesartan is ineffective in children.

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## Aldosterone Receptor Antagonists

Aldosterone receptor antagonists (ARAs) exert their BP-lowering effects by competitively blocking mineralocorticoid receptor sites in the distal renal tubule, increasing sodium chloride and water excretion while conserving potassium and hydrogen. In addition, they may block the effect of aldosterone on arteriolar smooth muscle.

In recent years, there has been an increased understanding of the role of aldosterone on overall cardiovascular health in adults. Beyond the traditional sodium-retaining effect of aldosterone, it is now clear that the hormone may activate receptors in multiple other organs including the heart, brain, and blood vessels ultimately leading to inflammation and fibrosis (Schiffrin 2006). This knowledge, in combination with emerging adult data showing a decrease in mortality in patients with severe heart failure treated with aldosterone blockade (Pitt et al. 1999, 2003), has sparked renewed interest in this drug class.

Currently, there are two available ARAs, spironolactone and eplerenone. Spironolactone has been available for decades; however, published data regarding efficacy and safety in the treatment of pediatric hypertension remains limited. It is a classic example of how experience in adult patients was adapted for treatment of childhood hypertension (Loggie 1969). Eplerenone is a newer, selective ARA with fewer endocrinologic side effects than spironolactone. In a recent trial, the antihypertensive effect of eplerenone was evaluated in pediatric patients 4–17 years of age (Li et al. 2010). Reductions in both systolic and diastolic BP were achieved on therapy; however, this reached statistical significance only in the high-dose group. No dose-response effect was demonstrated. FDA review of the trial found the suggestion of a beneficial effect in children with hypertension to be marginal, and, therefore, pediatric labeling was not granted.

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## Beta-Adrenergic Antagonists

The  $\beta$ -adrenergic antagonists are a large class of medications with heterogeneous pharmacologic properties. They act by blocking stimulation of  $\beta$ 1- and  $\beta$ 2-adrenoreceptors of the nervous system, resulting in decreased BP by a number of mechanisms, including a reduction in cardiac output, a diminution of renin release, a decrease in central nervous system sympathetic outflow, and a presynaptic blockade that inhibits catecholamine release (Kaplan and Victor 2010). All currently available agents antagonize cardiac  $\beta$ 1-receptors

competitively but vary in the degree of  $\beta$ 2-receptor blockade in extra cardiac tissues. In addition, there are other  $\beta$ -adrenergic antagonists that have vasodilating properties either through concomitant alpha blockade or through the generation and release of nitric oxide. With this in mind, it is not surprising that there is considerable within class variability with respect to tolerability and side effect profiles (Manrique et al. 2009).

Most  $\beta$ -adrenergic antagonists no longer had patent protection when the FDAMA was enacted. Hence, few drugs in this class have been studied rigorously in hypertensive children, and evidenced-based data with respect to efficacy and safety in this population are lacking. Two notable exceptions are metoprolol and bisoprolol, the latter of which was studied in a combination preparation with hydrochlorothiazide (HCTZ). Using an extended-release formulation, the pediatric metoprolol trial demonstrated a significant reduction in systolic BP in those treated at moderate (1 mg/kg) and high (2 mg/kg) doses and a significant reduction in diastolic BP at high dose (Batisky et al. 2007). In addition, the placebo-corrected change in diastolic BP exhibited a statistically significant dose-response relationship. A 52-week open-label extension revealed a favorable tolerability and safety profile. In the bisoprolol/HCTZ study, treatment groups did exhibit significant reductions in systolic and diastolic BP (Sorof et al. 2002). However, there was large placebo effect and the percentage of children who achieved BP less than the 90th percentile was not significantly different in the bisoprolol/HCTZ group compared to the placebo group. Of note, the bisoprolol/HCTZ group had fewer overall adverse events and fewer serious adverse events than subjects treated with placebo.

Propranolol was the first  $\beta$ -adrenergic antagonist available in the United States and, historically, is the most extensively used in children and adolescents (Robinson et al. 2005). However, the availability of controlled clinical trials of this agent in children is lacking. There are published reports describing the use of propranolol in children (Griswold et al. 1978; Bachmann 1984; Friedman et al. 1987), though these involve a limited number of subjects making it difficult to

draw conclusions with respect to efficacy and safety. It should be noted that propranolol is available in a commercially prepared oral solution.

Vasodilatory  $\beta$ -adrenergic antagonists have recently garnered much attention as potential alternatives to traditional beta-blockers in the management of hypertension in the adult population. Carvedilol and labetalol cause vasodilation through  $\alpha$ 1-receptor blockade, and nebivolol induces endothelium-dependent vasodilation by stimulating nitric oxide activity (Pedersen and Cockcroft 2007). Whereas conventional  $\beta$ -adrenergic antagonists tend to raise peripheral vascular resistance (PVR) and reduce cardiac output (CO), these reduce PVR while maintaining or improving CO. At this point, none of these agents has been specifically studied for hypertension in the pediatric population, though FDA-approved pediatric dosing guidelines do exist for carvedilol in the treatment of heart failure.

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## Calcium Channel Blockers

Calcium channel blockers (CCBs) are a pharmacologically heterogeneous class of drugs that have a long history of use in the treatment of both adult and childhood hypertension. CCBs antagonize the L-type voltage-dependent slow channel of the cellular membrane of myocardial and vascular smooth muscle, ultimately resulting in decreased contraction and a reduction of BP through dilation of the peripheral arteries (Robinson et al. 2005).

CCBs are divided into two classes: the tertiary amines and the dihydropyridines. The tertiary amines, diltiazem and verapamil, are used primarily as antiarrhythmic agents because of their effect on AV nodal conduction, although both are effective antihypertensive agents as well. Neither diltiazem nor verapamil has been specifically studied in hypertensive children. Dihydropyridine CCBs commonly used in pediatric hypertension include nifedipine, isradipine, felodipine, and amlodipine, of which only felodipine and amlodipine have been granted pediatric exclusivity.

Nifedipine is available in a short-acting and extended-release formulation, neither of which

has been rigorously studied in children. The published literature regarding the use of nifedipine in hypertensive pediatric patients is largely restricted to the use of the short-acting agent in the setting of hypertensive urgencies (Dilmen et al. 1983; Evans et al. 1988; Roth et al. 1986; Siegler and Brewer 1988). More recently, the use of this agent has been avoided for acutely elevated BP as it has been associated with a precipitous drop in BP and an increased risk for myocardial infarction, stroke, and death in the adult population (Grossman et al. 1996). Pediatric data suggest that short-acting nifedipine may be used safely with judicious dosing in otherwise healthy children (Egger et al. 2002; Blaszak et al. 2001); however, many recommend abandoning its use in children given the availability of safer alternatives (Truttmann et al. 1998; Flynn 2002). There is a paucity of published reports describing the use of nifedipine for the treatment of chronic hypertension in children. One study compared the efficacy and tolerability of extended-release nifedipine and amlodipine in a small cohort of pediatric renal transplant recipients (Silverstein et al. 1999). The two drugs were noted to have comparable efficacy, though nifedipine appeared to be associated with more side effects, particularly gingival hyperplasia. Based on published reviews, it seems safe to assume that extended-release nifedipine is commonly used in children for the management of chronic hypertension (Sahney 2006). One factor limiting the use of extended release nifedipine is the necessity to swallow a pill, which may not be feasible in younger children.

As with nifedipine, efficacy and safety data for isradipine in childhood hypertension are limited. A number of single-center case series have been published detailing isradipine use in children (Flynn and Warnick 2002; Strauser et al. 2000; Johnson et al. 1997). Most of the children included in these studies were hospitalized with new-onset secondary hypertension. In this population, isradipine effectively lowered systolic and diastolic blood pressure with a low rate of adverse events. Most children required dosing three to four times daily, which may limit isradipine use for long-term therapy. Acutely, isradipine appears

to be a safe and effective medication for reduction of severe hypertension, and its use has been advocated over nifedipine in children (Miyashita et al. 2010). A stable extemporaneous solution can be compounded that allows for appropriate dosing in infants and young children.

Felodipine use in childhood hypertension has been more rigorously studied than either nifedipine or isradipine. In a single-center crossover study, once-daily dosing of felodipine was found to be more effective than extended-release nifedipine in children with hypertensive renal disease as assessed by ambulatory BP monitoring (Moncica et al. 1995). In addition, compliance was significantly better in those treated with felodipine. In the industry-sponsored felodipine trial, 5 mg resulted in significantly improved diastolic BP values over placebo; however, no dose-response relationship was observed, and no significant difference in BP values was noted at lower (2.5 mg) or higher (10 mg) doses when compared to placebo (Trachtman et al. 2003). This study was plagued by a number of design flaws that likely contributed to the failure to demonstrate a dose response. Over the 17-week study period, felodipine was well tolerated with few adverse events and a lower incidence of peripheral edema than in adults.

Considerably more data are available regarding the use of amlodipine in childhood hypertension than the other CCBs. In single-center pediatric studies, amlodipine consistently demonstrated efficacy in reducing BP in patients with both primary and secondary hypertension (Tallian et al. 1999; Flynn et al. 2000; Rogan et al. 2000; von Vigier et al. 2001; Andersen et al. 2006). Amlodipine was reported to provide sustained BP control on stable dosing with favorable safety and tolerability over a mean follow-up duration of 20 months (Flynn 2005). Population pharmacokinetic studies demonstrated clearance and distribution characteristics in older children that were similar to adults. Plasma concentrations were similar whether amlodipine was dosed once or twice daily, suggesting that once-daily regimens were likely sufficient in children (Flynn et al. 2006). In the industry-sponsored clinical trial, amlodipine

produced significantly greater BP reductions than placebo with a dose-response effect on systolic and diastolic BP at doses greater than 0.06 mg/kg/day (Flynn et al. 2004). In addition, an extemporaneous suspension has been studied that has been shown to be stable for 3 months with bioequivalence that is not different from the tablet (Lyszkiewicz et al. 2003; Nahata et al. 1999). Instructions for formulation of the suspension are available on the FDA-approved labeling.

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## Diuretics

Diuretics exert their effect by promoting urine production through a reduction in renal tubular sodium reabsorption. There are a number of agents available that act on different sites of the nephron, with variable degrees of potency. While diuretics are commonly used in adults, often as first-line agents, their use is more limited in children. No controlled clinical trials examining diuretic use in pediatric hypertension have been conducted. Dosing guidelines exist for many diuretics with several available in suspension form; however, the clinical indication is for the treatment of edema, not hypertension.

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## Direct Vasodilators

Vasodilators such as minoxidil and hydralazine reduce BP by relaxing arterial wall smooth muscle cells with a resultant decrease in peripheral vascular resistance. Several single-center case series have been published describing the use of minoxidil in children suggesting efficacy in the treatment of severe childhood hypertension (Sinaiko and Mirkin 1977; Puri et al. 1983; Strife et al. 1986). No controlled clinical trials in children have been performed, and long-term safety data is lacking. Due to hypertrichosis in those with long-term exposures, minoxidil use in children has generally been reserved for those with severe refractory hypertension. There is notably little data with respect to efficacy and safety of hydralazine in childhood hypertension.



## Other Antihypertensive Agents

No pediatric trials have been conducted for alpha-blockers or central-acting agents, and very little has been reported with respect to efficacy or safety of these agents in children. Alpha blockers play an important role in the treatment of some disorders, such as pheochromocytoma, though they have limited utility in pediatrics given their poor tolerability profile. Clonidine, the most widely used central-acting agent, inhibits central sympathetic outflow resulting in decreased peripheral vascular resistance. Small studies suggest that clonidine may be an effective agent for the treatment of childhood hypertension (Falkner et al. 1983); however, there is a poor side effect profile and a risk for rebound hypertension when the medication is discontinued suddenly.

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## Future Directions in Drug Studies

Despite the considerable increase in the number of drugs with FDA-approved pediatric labeling, there is evidence that a significant number of pediatric hypertensive patients are treated with medications that are neither labeled for nor recommended for use in children. Using a nationwide commercial insurer database, Welch et al. (2012) found that 7% of drugs prescribed to children studied were neither labeled for use nor considered recommended for use in the pediatric population. In the youngest population studied (<6 years), 29% of drugs used were not indicated for use in that age group. Additionally, a recent Cochrane review has highlighted gaps in data regarding antihypertensive efficacy and safety that have not been completely addressed by recent trials (Chaturvedi et al. 2014). The review included 21 pediatric trials, many of which are industry-sponsored trials cited earlier in this chapter and concluded that the quality of evidence supporting the antihypertensive efficacy of various drug classes including ACE-I, ARB, CCB, and  $\beta$ -adrenergic agonists was generally low (Chaturvedi et al. 2014). The authors emphasized the need for more long-term trials to further

evaluate the efficacy of antihypertensive agents with respect to not only reduction in blood pressure but also reduction of target-organ damage (Chaturvedi et al. 2014). With these concerns in mind, it is safe to assert that much more work must to be done to increase awareness among physicians about the availability of labeling information to guide pediatric antihypertensive prescribing practices. In addition, more effort is necessary to encourage the rigorous study of those drugs that are used but continue to lack pediatric labeling.

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## Targeted Approach to Therapy

The decision to initiate antihypertensive medications in any child should not be taken lightly. Although there is a growing body of evidence with respect to the safety and tolerability of particular agents, follow-up studies are limited in duration and little is known regarding the impact of long-term pharmacologic therapy on growth and cognitive development. Additionally, it is likely that, once started, the medication will need to be continued for decades. In an effort to maximize benefit, a targeted approach to therapy is generally advocated. Given the higher prevalence of secondary hypertension in children, the pathophysiologic mechanism of hypertension can often be identified. In some cases, this facilitates selection of a specific therapeutic agent. In patients with concomitant diseases, such as diabetes, a specific drug may be particularly beneficial. In addition to assessing presumed benefit and likelihood of response to an agent, it is also important to consider potential adverse effects prior to initiating therapy. For example, non-cardioselective beta-adrenergic blockers are generally avoided in those with reactive airway disease due to an increased risk of bronchospasm (Prichard et al. 2001). In addition, ACE inhibitors/ARBs are absolutely contraindicated in pregnancy due to the potential for fetopathy (Bullo et al. 2012), and appropriate counseling regarding contraception or sexual abstinence is required prior to initiation in girls of childbearing years. The following sections

**Table 4** Indications for targeted drug therapy

Condition	Drug
Renovascular hypertension	Diuretic, Vasodilator ACE-I, ARB (if not bilateral disease)
Coarctation of aorta	Beta-agonist
Chronic kidney disease	ACE-I, ARB
Obesity related hypertension	ACE-I, ARB
Hypertensive athlete	ACE-I, ARB, CCB

*ACE-I* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *CCB* calcium channel blocker

describe clinical situations where a specific class of antihypertensive agents may be particularly advantageous. Indications for targeted therapy with corresponding medications are summarized in Table 4.

## Renovascular Hypertension

Renovascular hypertension is a secondary form of hypertension that results from narrowing of one or both of the renal arteries or branches. In the setting of renal artery stenosis, perfusion to either the entire kidney or a portion of it is compromised, stimulating the release of renin and subsequent upregulation of the entire renin-angiotensin-aldosterone system (RAAS) (Garovic and Textor 2005a, b). In this setting, angiotensin blockades with ACE inhibitors or ARBs are rational choices to treat blood pressure elevation. Unfortunately, such therapy carries a risk of acute kidney injury due to relaxation of the efferent arteriole and concomitant reduction in glomerular capillary hydrostatic pressure. For this reason, bilateral renal artery stenosis is generally considered an absolute contraindication to ACE inhibitor or ARB therapy. In rare cases, angiotensin blockade may be employed in those with bilateral disease, though this should be undertaken under close supervision of a hypertension specialist experienced in treating this population. If disease is unilateral or isolated to segmental renal arteries, these medications are generally safe and particularly effective. Gradual dose titration and judicious monitoring of renal function tests and potassium balance is

mandated. Given the increased renin secretion, there is always sodium retention and volume overload in patients with renovascular hypertension; therefore, diuretics and vasodilators, such as calcium channel blockers, also play important roles in therapy, especially as initial agents when bilateral disease is present. In addition, increased sympathetic nervous system activity is known to occur in patients with renovascular hypertension (Johansson and Friberg 2000). With this in mind, alpha- and beta-adrenergic blockers as well as central-acting agents, such as clonidine, are often utilized in those who require multidrug regimens.

## Coarctation of the Aorta

Coarctation of the aorta occurs in 1 of every 2500 live births, accounting for 6–8% of all congenital heart defects (Kenny and Hijazi 2011). Hypertension is a common feature that occurs early, at the time of diagnosis, as well as late, sometimes decades following intervention to correct the obstruction. The exact pathophysiology leading to blood pressure elevation has not been fully elucidated, though upregulation of the RAAS system and sympathetic activation has been described. Surgical or endovascular correction represents the mainstay of therapy, with early intervention associated with improved long-term outcomes. Traditionally, beta-adrenergic blockade has been advocated in the period before repair, as these agents are believed to reduce the degree of acute post-intervention hypertension (Gidding et al. 1985) and are less likely to cause acute kidney injury than angiotensin blockade. In those in whom hypertension persists after correction, beta-blockade is typically continued, though treatment with ACE inhibitors or ARBs may also be safe and effective in those with no residual obstruction. In addition, there is some evidence that ACE inhibitors may have the added benefit of improving endothelial function and reducing pro-atherogenic inflammatory cytokines in those with successfully repaired aortic coarctation, even in the absence of systemic hypertension (Brili et al. 2008).

## Chronic Kidney Disease

Hypertension is common in children with CKD. Recent analysis of data from the ongoing Chronic Kidney Disease in Children Study (CKiD) cohort revealed a prevalence of 54%. (Flynn et al. 2008). Uncontrolled hypertension, hyperfiltration, and proteinuria are known risk factors for accelerated renal decline in adult patients (Klag et al. 1996; Iseki et al. 2003; Locatelli et al. 1996). There is a preponderance of evidence that angiotensin blockade slows the progression of renal decline in adults, likely secondary to antihypertensive, anti-proteinuric, and anti-fibrotic properties (Maschio et al. 1996; Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia) 1997; Jafar et al. 2001). Relative to adult studies, there is a dearth of pediatric data regarding similar benefits in children. However, there is evidence that ACE inhibitors and ARBs may have superior antihypertensive effect in this population. An analysis of baseline BP characteristics from CKiD found that there was an increased prevalence of uncontrolled BP in participants receiving antihypertensive therapy that did not include an ACE inhibitor or ARB (Flynn et al. 2008). Furthermore, a report of ABPM findings in 332 children 1 year after entry to CKiD found that individuals whose antihypertensive regimen included an ACE inhibitor were 89% more likely to have a normal ABPM than those who did not report using an ACE inhibitor (Samuels et al. 2012). Although not specifically designed to examine the benefits of angiotensin blockade, the ESCAPE trial found that intensive BP control with a medication regimen that included the ACE-inhibitor ramipril led to significantly fewer patients reaching the primary end point, defined as 50% reduction in GFR or progression to ESRD (Wuhl et al. 2009). It is important to note that this benefit was not solely related to treatment with ramipril but rather to achieving a target 24-h ambulatory mean arterial pressure <50th percentile. Overall, there appears to

be general agreement that ACE inhibitors and ARBs should be considered first-line therapy for hypertensive therapy in children with CKD, particularly those with concomitant proteinuria. Given the risk for depressed GFR and hyperkalemia in this population, careful monitoring of electrolyte balance and renal function tests is mandatory.

## Primary Hypertension/Obesity-Related Hypertension

Primary hypertension is an increasing problem in childhood, largely the result of the ongoing obesity epidemic. In the United States, 17–18% of children and adolescents are now classified as obese, defined as a body mass index (BMI)  $\geq$  95th percentile for age and gender (Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report 2011; Ogden et al. 2012). This trend has been observed in other countries as well, including Italy, Spain, Greece, China, India, Brazil, and South Africa (Lazzeri et al. 2008; Valdes Pizarro and Royo-Bordonada 2012; Kollias et al. 2011; Midha et al. 2012; Wang and Lobstein 2006). The impact of obesity on childhood blood pressure has been studied extensively. A screening study in the Houston public schools demonstrated that hypertension was present in up to 11% of obese children compared to 2–3% of children with a BMI  $\leq$  75th percentile (Sorof et al. 2004). Furthermore, obesity confers increased risk of additional cardiovascular comorbidities, including insulin resistance and dyslipidemia. The coexistence of abdominal obesity, hypertension, insulin resistance, and dyslipidemia constitutes the metabolic syndrome, which is associated with atherosclerosis and is a strong independent predictor of adverse cardiovascular events in adults (Schillaci et al. 2004). In the United States, the reported prevalence of the metabolic syndrome in adults and adolescents is 25% (Ford et al. 2002) and 4.5% (Ford et al. 2008), respectively. Therefore, regular screening for dyslipidemia and impaired glucose tolerance in the obese hypertensive child should be performed.

The pathophysiology of obesity-related hypertension is complex, and an extensive discussion is beyond the scope of this chapter. Important mechanisms likely include hyperinsulinemia and increased leptin levels, both of which lead to increased activity of the sympathetic nervous system (SNS) (Landsberg et al. 2013). Activation of the RAAS, a result of increased SNS activity and increased production of angiotensinogen in adipose tissue, is also believed to play a central role (Landsberg et al. 2013). Other factors, including decreased natriuretic peptides (Sarzani et al. 2008) and endothelial dysfunction (Caballero 2003), contribute to impaired sodium excretion and increased vascular resistance.

Some obese patients may be managed successfully with therapeutic lifestyle interventions, including extensive counseling regarding the importance of appropriate dietary choices, regular exercise, and weight loss. Unfortunately, success may be difficult to achieve with this approach alone and treatment with antihypertensive medication is often required. As alluded to earlier, choice of an initial agent in this setting is typically based on provider preference. Though pediatric studies are lacking, ACE inhibitors, ARBs, CCBs, beta-blockers, and thiazide diuretics are all effective in lowering BP in obese adults (Allcock and Sowers 2010). There is emerging evidence that inhibition of the RAAS may be of particular benefit in this population. In adults, ACE inhibitors and ARBs appear to reduce the risk of new onset diabetes mellitus and may also increase insulin sensitivity (Prabhakar 2013; Sharma 2008; Murakami et al. 2013). Based on the underlying mechanisms leading to blood pressure elevation as well as obesity-related comorbidities, initial therapy with ACE inhibitors or ARBs has been advocated (Landsberg et al. 2013). In the author's opinion, this is a reasonable approach in pediatric obesity-related hypertension as well. CCBs are an acceptable alternative for initial therapy. Beta-blockers and thiazide diuretics should be avoided as first-line agents as they are known to alter glucose metabolism, predisposing to insulin resistance and potentially increasing the rate of development of diabetes (Mancia et al. 2006).

Presently, appropriate selection of an initial medication in the child with non-obesity-related primary hypertension is less clear. In the adult population, evidence has emerged to suggest that a renin-guided approach in patients with primary hypertension may be beneficial. Laragh postulates that long-term BP control is sustained by two intervening forces: (1) the sodium-volume (V) content and (2) plasma renin-angiotensin vasoconstrictor (R) activity (Laragh and Sealey 2011; Laragh 2001). With this in mind, the plasma renin level may be used to determine the relative involvement of V and R factors in determining BP, making it possible to identify an appropriate intervention. Suppressed-renin volume-dependent hypertension should be treated with an anti-V drug (diuretic, CCB, mineralocorticoid receptor antagonist), and high-renin vasoconstrictive hypertension should be treated with an anti-R drug (ACE inhibitor, ARB,  $\beta$ -adrenergic antagonist). Recent data suggest that such an approach is efficacious (Egan et al. 2009; Turner et al. 2010). Moreover, there is also evidence that selection of a "wrong" drug (an anti-V drug for R hypertension or an anti-R drug for V hypertension) can lead to a paradoxical rise in BP in adults (Alderman et al. 2010). There is no body of evidence that such an approach is effective in pediatric patients, and further studies in this age group are warranted.

## The Hypertensive Athlete

Hypertension is the most common cardiovascular disease seen in individuals who engage in competitive sports (Maron and Zipes 2005). As in other pediatric patients, confirmed hypertension in the young athlete should prompt an appropriate evaluation for an underlying etiology. In addition to typical considerations, the possibility of exogenous sources contributing to BP elevation should be thoroughly explored. In general, performance-enhancing drugs (PEDs), including stimulants, anabolic steroids, growth hormone, and erythropoiesis-stimulating agents, have the potential to increase BP. In the United States, the prevalence of illegal steroid use reported in the National Youth Risk Behavior Survey decreased

from 6.2% to 3.6% over the last decade (Eaton et al. 2012); however, this statistic may not capture the full scope of PED use. For example, a recent survey of 3575 young competitive athletes in Quebec revealed that 25.8% of respondents reported that they had used 1 or more of 15 substances restricted by the International Olympic Committee in the preceding 12 months (Goulet et al. 2010). Therefore, the importance of directed questioning in this regard cannot be over-emphasized. Discontinuation of any substance with the potential to increase BP should be encouraged prior to initiating antihypertensive medication.

If antihypertensive medications are deemed necessary, careful attention to potential side effects that may have particular relevance in athletes should be considered in selecting an optimal agent.

In general, diuretics and beta-blockers should be avoided. Diuretic use may impair exercise tolerance due to decreased intravascular volume, especially in the first weeks after initiation (Fagard 2007). Furthermore, diuretics may predispose the athlete to dehydration and electrolyte abnormalities. Both cardioselective and non-selective beta-blockers reduce maximal exercise capacity (Van Baak 1988). This is very likely the result of decreased cardiac output as well as altered lipolysis during activity (Van Baak et al. 1988; Vanhees et al. 2000). ACE inhibitors, ARBs, and CCBs, on the other hand, have a low side effect profile and have not been found to impact exercise tolerance. As a result, each is considered an acceptable option for use in the hypertensive athlete.

## Monogenic Forms of Hypertension

Impressive progress in genetics and molecular biology has led to the identification of a number of single-gene mutations resulting in hypertension. In each, the defective gene results in increased sodium reabsorption in the distal nephron resulting in volume expansion, increased cardiac output, and hypertension. This group of disorders should be considered in any child who is suspected of having secondary hypertension despite a negative evaluation for more common underlying etiologies. In addition, important laboratory clues are low renin levels, which is a common feature, as well as alterations in potassium and acid/base balance. Commercial testing is currently available for a number of these disorders, though an evaluation of distal tubular function and urinary steroid hormone profiling may be sufficient to establish a diagnosis. From a therapeutic standpoint, a high level of suspicion is important as the hypertension that results is typically readily treated with a medication targeted to the mechanistic defect leading to increased sodium reabsorption and often refractory to other medications. Two exceptions to this rule are autosomal dominant hypertension with brachydactyly and activating mineralocorticoid receptor mutation, both of which cause hypertension that may be refractory to standard medical management. A more extensive review of monogenic forms of hypertension is provided in ► [Chap. 7, “Monogenic and Polygenic Contributions to Hypertension.”](#) A summary of disorders with associated findings and indicated therapies is provided in [Table 5](#).

**Table 5** Typical features in monogenic forms of hypertension

	Inheritance pattern	Age	K	Renin	Aldo	Therapy
AME	AR	I, C, A	↓ or N	↓	↓	Spirinolactone, eplerenone
GRA	AD	I, C	↓ or N	↓	↓ or N	Amiloride, triamterene, glucocorticoids
CAH	AR	I	↓ or N	↓	↓	Spirinolactone, eplerenone
LS	AD	C, A	↓ or N	↓	↓	Amiloride, triamterene
GS	AD	A, C	↑ or N	↓	↑ or N	Thiazide

*AME* apparent mineralocorticoid excess, *GRA* glucocorticoid-remediable aldosteronism, *CAH* congenital adrenal hyperplasia, *LS* liddle syndrome, *GS* gordon syndrome, *AR* autosomal recessive, *AD* autosomal dominant, *I* infancy, *C* childhood, *A* adulthood, *N* normal, ↓ decreased, ↑ increased

## Conclusion

The prevalence of pediatric hypertension is increasing, and pediatricians are increasingly expected to provide appropriate therapeutic interventions. There is a growing body of pediatric specific data with respect to efficacy and safety of pharmaceutical therapies; however, much is still to be learned about their impact on long-term outcomes, including growth, cognitive development, as well as cardiovascular morbidity and mortality. When medications are required, a rational approach to selecting an appropriate agent with respect to pathophysiology, potential benefit, and likelihood for side effect is advocated.

## Cross-References

- ▶ [Ambulatory Blood Pressure Monitoring Methodology and Norms in Children](#)
- ▶ [Diagnostic Evaluation of Pediatric Hypertension](#)
- ▶ [Epidemiology of Primary Hypertension in Children](#)
- ▶ [Hypertension in Chronic Kidney Disease](#)
- ▶ [Monogenic and Polygenic Contributions to Hypertension](#)
- ▶ [Nonpharmacologic Treatment of Pediatric Hypertension](#)
- ▶ [Obesity Hypertension: Clinical Aspects](#)
- ▶ [Primary Hypertension in Children](#)
- ▶ [Renovascular Hypertension, Vasculitis, and Aortic Coarctation](#)
- ▶ [Secondary Forms of Hypertension in Children: Overview](#)
- ▶ [Sequelae of Hypertension in Children and Adolescents](#)

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## Abstract

Severe, symptomatic hypertension occurs infrequently in childhood but when present often signifies a life-threatening emergency. The clinician needs to approach this situation with a sense of urgency to reduce blood pressure (BP) and limit end-organ damage while avoiding overly aggressive therapy, which may also lead to ischemia and further injury. This chapter discusses the causes, pathophysiology, evaluation, and treatment of severe hypertension.

## Keywords

Hypertensive Emergencies • Hypertensive urgencies • Severe hypertension • Posterior reversible leukoencephalopathy syndrome • Cerebral autoregulation

## Abbreviations

BP	Blood pressure
JNC	Joint National Committee.
ECG	Electrocardiogram.
PRES	Posterior reversible leukoencephalopathy syndrome.
IV	Intravenous.

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## Introduction

Severe, symptomatic hypertension occurs infrequently in childhood but when present often signifies a life-threatening emergency. The clinician needs to approach this situation with a sense of urgency to reduce blood pressure (BP) and limit end-organ damage while avoiding overly aggressive therapy, which may also lead to ischemia and further injury. This chapter discusses the causes, pathophysiology, evaluation, and treatment of severe hypertension.

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## Definitions of Hypertensive Crises, Emergencies, and Urgencies

The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents classifies hypertension in childhood into two stages (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). Stage 1 hypertension is designated for blood pressure levels from the 95th percentile to 5 mmHg above the 99th percentile for age, gender, and height, while Stage 2 hypertension is designated for levels above the 99th percentile plus 5 mmHg. Recently published guidelines from the European Society of Hypertension also recognize this staging system for younger patients but suggest that hypertension be graded with absolute levels for those aged 16 years or above (Lurbe et al. 2016). Stage 1 hypertension by these guidelines is 140–159/90–99, and Stage 2 hypertension is  $\geq 160/100$ . Finally, the 2017 American Academy of Pediatrics (AAP) clinical practice guideline further revised the staging system and adopted adult cut-points for adolescents  $\geq 13$  years of age (Flynn et al. 2017). The purpose of these staging systems is to help distinguish mild hypertension from more severe hypertension where more immediate and extensive evaluation is indicated.

School-based screenings report a prevalence of Stage 1 hypertension in 2.6% and Stage 2 hypertension in 0.6% of adolescent students when blood pressure was measured on three separate occasions (McNiece et al. 2007). While the width of the blood pressure range in Stage 1 hypertension is only 12–15 mmHg, individuals with Stage 2 hypertension may have a blood pressure level just a few or many mmHg above the Stage 2 limit. Patients with Stage 1 or Stage 2 hypertension may be asymptomatic or have a range of clinical signs or symptoms (Croix and Feig 2006).

The terminology used to further categorize severe hypertension as a hypertensive crisis, emergency, or urgency has not been rigorously defined in childhood. The report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Hypertension, JNC

7, considers blood pressure values above 180/120 in adults to constitute a “hypertensive crisis” (Chobanian et al. 2003; Padilla Ramos and Varon 2014). This is a value 20 mmHg above the lower limit for Stage 2 hypertension in adults. While there is no absolute level of blood pressure that constitutes a hypertensive crisis in childhood or adolescence, values would be expected, as with adults, to usually exceed the Stage 2 limit. The 2017 AAP guideline proposes that a BP level of 30 mmHg or more above the 95th percentile should be used to denote children and adolescents at risk of development of severe hypertensive sequelae (Flynn et al. 2017).

Hypertensive emergencies and hypertensive urgencies are considered to be two forms of a hypertensive crisis. Severe hypertension with the presence of life-threatening symptoms or target-organ injury defines a hypertensive emergency. In a hypertensive urgency, the blood pressure could be similarly elevated, but less significant symptoms would be present and no acute target-organ injury (Padilla Ramos and Varon 2014). For example, a hypertensive child presenting with encephalopathy or heart failure would be considered as experiencing a hypertensive emergency, while a hypertensive teenager with a headache and vomiting would be classified as experiencing a hypertensive urgency. Perioperative hypertension is also considered to be a hypertensive urgency (Varon and Marik 2008).

Other terms have also been used to describe severe hypertension. “Accelerated hypertension” is used to describe a recent significant rise over baseline blood pressure that is associated with target-organ damage. “Malignant hypertension” describes the association of elevated BP in association with retinopathy. This term, however, has been removed from National and International Blood Pressure Control guidelines, and hypertension multi-organ damage (MOD) has been suggested to better reflect clinical situations of acute hypertension with impairment of at least three organ systems considered to be a true emergency (Cremer et al. 2016). Confusion regarding the definitions and use of these terms has led some authors to avoid the distinction between hypertensive emergencies or urgencies and

consider a classification scheme of severe hypertension with or without severe symptoms or end-organ injury (Adelman et al. 2000; Flynn and Tullus 2009).

### Organ Systems Susceptible to Hypertensive Injury

Damage to organs in a hypertensive emergency may involve the brain (seizures, focal deficits, hemorrhage), eye (papilledema, hemorrhages, exudates), kidneys (renal insufficiency), and heart (congestive heart failure). Reports dating back to the 1960s have demonstrated an association between severely elevated blood pressure and hypertensive target-organ damage in children. In 1967, Still and Cottom reviewed their experience with 55 children with severely elevated blood pressure (diastolic BP > 120 mmHg) and evidence of cardiomegaly on clinical exam or left ventricular hypertrophy on electrocardiogram (ECG) (Still and Cottom 1967). Neurologic complications (facial palsy, convulsions, cerebrovascular lesions) were present in 1/3 of these patients and papilledema in 36%. Unfortunately, due to the lack of effective therapy, 31 of 55 (56%) died as a result of complications from hypertension. In a 1992 report by Deal, 82 of 110 children (75%) requiring “emergent” treatment for an average blood pressure of 180/127 mmHg had evidence of injury to at least one organ system (Table 1). Fortunately, long-term outcome was improved with only 4% experiencing sustained neurologic

damage (Deal et al. 1992a). Another report from 1987 on 27 children and adolescents with renovascular hypertension with mean BP at presentation of 172/114 mmHg (age 5 month to 20 year) found that 85% had evidence of target-organ abnormalities (Daniels et al. 1987). Eighteen of 27 (66%) had left ventricular hypertrophy by ECG, 16 of 27 (60%) had retinal vascular lesions, and three of 27 (11%) had renal failure.

A recent study evaluating the severity of hypertension and organ injury found that patients with nausea/vomiting and visual impairment had a higher degree of systolic blood pressure elevation (29–46%) above the Stage 2 hypertension limit (99th percentile +5 mmHg) as compared to those with a hypertensive crisis but without these symptoms (17–19%) (Wu et al. 2012). Patients with altered consciousness had higher percentage for systolic and diastolic elevation (26–102%) than those with clear consciousness (19%). The authors concluded that SBP elevation 20% above the Stage 2 hypertension limit might indicate a critical point for organ injury in children with a hypertensive crisis.

### Pathophysiology

One of the key homeostatic mechanisms to prevent organ injury is vascular autoregulation. While present in many tissues, autoregulation of cerebral blood flow is the best studied (Strandgaard et al. 1973; Strandgaard and Paulson 1984). This mechanism attempts to maintain a constant cerebral blood flow in the presence of a broad range of perfusion pressures. This constancy occurs due to cerebral arteriolar vasoconstriction with increasing perfusion pressure and vasodilatation with decreasing perfusion pressure. Other factors influencing cerebral blood flow include cerebral metabolic demand and blood oxygen and carbon dioxide content (Vavilala et al. 2002a). In adults, autoregulation appears to be present over the mean arterial pressure range from 60 to 150 mmHg (Paulson et al. 1989). Autoregulation appears early in development and is present in later fetal and neonatal lambs as well as neonatal dogs and humans (Volpe 2008;

**Table 1** Signs and symptoms of hypertensive emergencies

Hypertensive retinopathy	27%
Hypertensive encephalopathy	25%
Convulsions	25%
Left ventricular hypertrophy	13%
Facial palsy	12%
Visual symptoms	9%
Hemiplegia	8%
Cranial bruits	5%
BP > 99th% without organ damage	24%

BP blood pressure

Adapted from Deal et al. (1992a)

Pryds and Edwards 1996; Fyfe et al. 2014). While the autoregulation limits in the human preterm and full-term newborn have not been established with certainty, the approximate range appears to be from 25 to 50 mmHg mean arterial pressure (Volpe 2008; Vutskits 2014). The autoregulatory plateau appears to be narrower in the newborn and increases with maturation. Autoregulation is rendered inoperative by factors leading to pronounced cerebral vasodilatation (hypercarbia, hypoxia, hypoglycemia, postasphyxial state). In these situations, cerebral blood flow becomes pressure passive, increasing susceptibility to hyperperfusion with increased cerebral perfusion pressure and ischemia with lower perfusion pressure (Volpe 2008).

In adults with uncontrolled chronic hypertension, there is a shift in the autoregulatory curve, providing constant cerebral blood flow at higher mean arterial pressures (Paulson et al. 1989). This shift may develop as a result of structural changes in the cerebral vasculature. While protecting against hyperperfusion at severely elevated blood pressure, this shift in the limits of autoregulation may lead to cerebral ischemia if blood pressure is rapidly lowered to a normotensive level. In acute hypertension, this shift in the autoregulatory curve has not occurred, making individuals more susceptible to hyperperfusion states at high pressures but less susceptible to ischemia when BP is rapidly reduced to the normal range. While differences exist in cerebral autoregulation between healthy boys and girls and adolescents and adults (Vavilala et al. 2002b; Vavilala et al. 2005; Tontisirin et al. 2007), the effects of chronic hypertension on developmental differences in cerebral autoregulation during childhood and adolescence remain largely unknown (Sharma et al. 2010). Reduced change in cerebral blood flow in response to hypercapnia has been recently described in untreated hypertensive children, suggesting deranged vasodilator reactivity as in adults (Wong et al. 2011).

When blood pressure exceeds the upper limits of the autoregulatory range, the compensatory response of vasoconstriction is inadequate, and cerebral blood flow increases proportionately with the mean arterial pressure. This leads to

forced vasodilatation, endothelial dysfunction, and edema formation as fluid is forced thru the capillary walls of the blood-brain barrier resulting in the development of hypertensive encephalopathy (Gardner and Lee 2007). This impairment in autoregulation has been demonstrated in severely hypertensive adults (Immink et al. 2004), and studies have demonstrated differential effects of antihypertensive agents on cerebral blood flow during blood pressure reduction (Immink et al. 2008).

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## Etiologies of Severe Hypertension

In contrast to adults where uncontrolled primary hypertension is the most common etiology of hypertensive emergencies, severe hypertension in children is generally considered to be secondary to disorders of the kidney, heart, or endocrine systems (Groshong 1996; Fivush et al. 1997; Chandar and Zilleruelo 2012; Baracco and Mattoo 2014; Stein and Ferguson 2016). Older case series have reported renal problems as the cause of hypertensive emergencies or urgencies in children in over 80% of patients (Deal et al. 1992b). With the increasing presence of primary hypertension in adolescence, this was reported recently as a more frequent etiology of severe hypertension in 47% of patients (Yang et al. 2012).

The etiologies of severe hypertension in children may vary with age and parallel the underlying causes of hypertension in each age group (Constantine and Linakis 2005). In neonates, renovascular disease secondary to an aortic or renal thrombus related to an umbilical artery catheter is a common cause of a hypertensive emergency as well as congenital renal anomalies and coarctation of the aorta. Outside of the newborn period, children may have renal parenchymal disease such as glomerulonephritis or reflux nephropathy or renovascular disease or endocrine disease. In adolescents, renal parenchymal diseases may also be seen, but additional causes of severe hypertension may include preeclampsia and drug intoxication (cocaine, amphetamines). While most adults presenting to the emergency department with severe hypertension have a

known diagnosis of hypertension (80%) (Bender et al. 2006), this would appear to be less common in childhood. Among adults with known hypertension, common reasons for severe BP elevation may include running out of medication (16%) and noncompliance (12%). These circumstances may also occur in childhood. Fluid overload in dialysis patients may be another cause for severe symptomatic hypertension (Sorof et al. 1999; Mitsnefes and Stablein 2005). In addition, abrupt withdrawal of either a beta-blocker or clonidine may result in “rebound” hypertension that may require urgent intervention (Geyskes et al. 1979).

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## Clinical Presentation

Children with severe hypertension may present with major symptoms or be asymptomatic (Croix and Feig 2006). After confirming that blood pressure has been measured with the proper size cuff and technique, the initial history and physical exam should focus on symptoms and signs of end-organ damage (Suresh et al. 2005; Baracco and Mattoo 2014). These may include central nervous system findings such as a change in behavior, seizures, vision changes, headache, altered mental status, confusion, focal weakness, or other neurologic signs. Orthopnea, shortness of breath, and edema may suggest congestive heart failure and hematuria, flank pain, “cola-colored” urine, and oliguria suggest renal disease.

Signs of end-organ damage may include those of hypertensive encephalopathy including lethargy, confusion, and coma (Wright and Mathews 1996; Hu et al. 2008). Facial nerve palsy has also been a CNS finding in children with a hypertensive emergency (Trompeter et al. 1982; Harms et al. 2000; Lewis et al. 2001; Tirodker and Dabbagh 2001). Hemorrhages or exudates and papilledema are frequently reported on fundoscopic exam (Skalina et al. 1983; Browning et al. 2001; Shroff et al. 2006; Williams et al. 2013). Tachypnea, pulmonary edema, a gallop rhythm, or a new heart murmur may suggest congestive heart failure. Additional signs may include peripheral edema suggesting fluid overload in

renal disease or an abdominal bruit suggesting renovascular hypertension. Exophthalmos may be associated with hyperthyroidism, and an abdominal mass may be seen with Wilms’ tumor, polycystic kidney disease, neuroblastoma, or congenital renal anomalies (Madre et al. 2006; Grinsell and Norwood 2009). Skin lesions such as café-au-lait spots and axillary freckling may suggest neurofibromatosis, which may be associated with renovascular hypertension or pheochromocytoma (Fossali et al. 2000). Diminished femoral pulses or reduced blood pressure in the legs suggests coarctation of the aorta (Farine and Arbus 1989). It is also important to look for signs of child abuse or other CNS trauma which may lead to hypertension through the development of increased intracranial pressure as these situations require therapy directed to preserve the cerebral perfusion pressure and should not be managed with antihypertensive medications (Pitfield et al. 2012).

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## Evaluation of Children with Hypertensive Crises

The evaluation of children with a hypertensive emergency should include a urinalysis to look for hematuria and proteinuria as evidence of underlying renal disease. Electrolytes, blood urea nitrogen, and creatinine should be measured to evaluate renal function. A complete blood count should be obtained to look for evidence of a microangiopathic hemolytic anemia (Belsha 2008). Adolescent girls should have a pregnancy test as preeclampsia may present with severely elevated blood pressure. A chest radiograph can screen for cardiac hypertrophy and vascular congestion. An echocardiogram is also helpful if heart failure is suspected or to look for left ventricular hypertrophy but should not delay the institution of therapy. A urine toxicology screen may be considered in some clinical settings as well as a renal ultrasound to evaluate for renal causes of hypertension (Tullus et al. 2010). If signs of encephalopathy are present, a computed tomography study of the head should be obtained to evaluate for cerebral edema, intracranial hemorrhage,



and stroke and to differentiate hypertensive encephalopathy from intracranial injury or mass lesion. More complex studies such as brain magnetic resonance imaging can be performed at a later date to evaluate for edema of white matter in the parieto-occipital regions as seen in posterior reversible encephalopathy syndrome (PRES) (Pavlakis et al. 1999; Kwon et al. 2001; Ishikura et al. 2006; Onder et al. 2007; Ishikura et al. 2012). If renovascular hypertension is suspected, other imaging modalities such as computed tomography angiography or magnetic resonance angiography or direct renal angiography may be considered after blood pressure is stabilized (Vade et al. 2002; Tullus et al. 2010).

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## Treatment of Severe Hypertension

The patient with a hypertensive emergency ideally should be managed in the intensive care unit where careful monitoring of blood pressure and neurologic status is possible. Blood pressure should be measured frequently, preferably by continuous intra-arterial monitoring. Initiation of treatment should not be delayed, however, for arterial cannulation. Frequent automated oscillometric or manual auscultatory readings may be adequate methods of blood pressure measurement initially. Noninvasive blood pressure measurements would be adequate as well for most patients with hypertensive urgency. A recent study reported better agreement between intra-arterial and Doppler ultrasound methods of BP measurement than with automated oscillometric readings, which were on average 10 mmHg lower than the other methods in hypertensive children (Holt et al. 2011). The airway, breathing, and circulation status of the patient should be frequently assessed and endotracheal intubation performed if mental status is depressed or in the presence of respiratory failure. Seizures should be stopped with anticonvulsants such as lorazepam. Two intravenous access lines should be present to prevent sudden loss of access for antihypertensive medications (Flynn and Tullus 2009).

A number of antihypertensive medications are available with established efficacy (Thomas

2011; Webb et al. 2014). Unfortunately, few have undergone rigorous testing in children, and less than half of current IV antihypertensive agents marketed in the USA have pediatric labeling (Flynn and Tullus 2009). There have been no randomized clinical trials of management of pediatric hypertensive emergencies to evaluate the optimal medication and rate or degree of blood pressure reduction. Most adult studies have also involved small numbers of patients with differing definitions for enrollment and outcome, treatment regimens, and length of follow-up (Messerli and Eslava 2008; Padilla Ramos and Varon 2014). Optimal treatment will remain more opinion than evidenced based until additional studies have been completed.

Adult and pediatric guidelines recommend that blood pressure be reduced in a controlled manner in hypertensive emergencies with continuous intravenous medications (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004; Chobanian et al. 2003; Lurbe et al. 2016; Flynn et al. 2017). Evidence supporting this view includes a report by Deal et al. comparing treatment complications in 53 children receiving intravenous labetalol and/or sodium nitroprusside infusion as compared with an earlier time period in which 57 children received intravenous bolus injection of diazoxide and/or hydralazine. Twenty-three percent of patients treated with bolus therapy experienced complications versus 4% of those treated with infusions. All seven children with permanent neurologic injury were treated with bolus therapy (Deal et al. 1992a).

The goal for chronic antihypertensive treatment in children is to reduce blood pressure to <90th percentile or <130/80 in an adolescent  $\geq 13$  years old. (Flynn et al. 2017). As noted above, children with chronic uncontrolled hypertension may be at much greater risk than those with acute hypertension to have decreased cerebral blood flow and ischemia with rapid normalization of blood pressure, so initial BP targets should be higher. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents recommends lowering blood pressure by  $\leq 25\%$  in the

first 8 h after presentation and then gradually normalizing the blood pressure over 26–48 h to prevent complications of treatment (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). Recently published guidelines from the European Society of Hypertension suggest that BP should be lowered by no more than 25% over the first 6–8 h, followed by a further gradual reduction over the next 24–48 h (Lurbe et al. 2016). In a hypertensive urgency, evaluation should occur immediately and treatment begun to lower BP over a course of hours to days with either intravenous or oral antihypertensive medications depending on the child's symptomatology.

Intravenous antihypertensive medications that have proven most useful in treating severe hypertension include nicardipine, labetalol, sodium nitroprusside, and hydralazine. Additional intravenous agents, which may be occasionally useful, include esmolol, fenoldopam, and possibly enalaprilat. Clevidipine is a newer agent with limited pediatric experience. Oral medications recommended for acute hypertensive urgencies include clonidine, isradipine, and minoxidil. Each of these will be reviewed below. Suggested doses for these agents can be found in Table 2.

Diazoxide, an intravenous direct vasodilator used frequently in the past by bolus injection (Kohaut et al. 1975; McLaine and Drummond 1971; McCrory et al. 1979), is no longer recommended as a first-line antihypertensive agent for hypertensive emergencies (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004) due to a long half-life and unpredictable duration of action (Flynn and Tullus 2009). Use of short-acting nifedipine has been abandoned in adults due to significant adverse events but continues to be used by some pediatric centers. While single and multicenter retrospective reviews have suggested this medication as safe and effective in children with in-hospital use (Blaszak et al. 2001; Egger et al. 2002; Yiu et al. 2004), others have pointed to difficulties in accurately dosing this medication, availability of other medications, and reports of adverse neurologic events as evidence against its continued use

(Flynn 2003; Calvetta et al. 2003; Leonard et al. 2001; Castaneda et al. 2005; Truttmann et al. 1998; Sasaki et al. 1997).

Sodium nitroprusside, a direct vasodilator of arteriolar and venous smooth muscle cells, has been used for treatment of severe hypertension in childhood since the 1970s (Gordillo-Paniagua et al. 1975; Luderer et al. 1977). The recommended dosage by continuous infusion is 0.53–10  $\mu\text{g}/\text{kg}/\text{min}$  (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). Nitroprusside acts by releasing nitric oxide, which dilates arterioles and venules and reduces total peripheral resistance. This decreases preload and afterload, allowing use of this agent for severe congestive heart failure as well as in severe hypertension. Use may result in modest tachycardia. Nitroprusside has a rapid onset of action within 30 s which results in rapid lowering of blood pressure. The antihypertensive effect disappears within a few minutes of stopping the medication. Toxicity occurs as a result of the metabolism of nitroprusside to cyanide and thiocyanate. Toxic accumulation of cyanide leads to development of metabolic acidosis with elevated lactate levels, tachycardia, altered consciousness, dilated pupils, and methemoglobinemia. Routine monitoring of cyanide levels is, however, no longer recommended due to the lack of correlation between levels and physical signs and symptoms (Thomas et al. 2009). A recent trial suggested good correlation between infusion rate and cyanide levels, but patients had few signs of cyanide toxicity (Hammer et al. 2015). Thiocyanate toxicity is suggested by symptoms of altered mental status, nausea, seizures, skin rash, psychosis, anorexia, or coma. The nitroprusside infusion should be discontinued if signs and symptoms of cyanide or thiocyanate toxicity are present. Thio-sulfate administration may facilitate the conversion of cyanide to thiocyanate by donating a sulfur group which may reduce the risk for cyanide toxicity but raise it for thiocyanate (Thomas 2011). Hydroxocobalamin is an agent approved for cyanide toxicity. Most authorities recommend limiting nitroprusside use to situations where no other suitable agents are available or to brief

**Table 2** Antihypertensive drugs for treatment of severe hypertension<sup>a</sup>

Drug	Class	Dose	Route	Comments
Emergencies (severe hypertension with life-threatening symptoms)				
Esmolol	β(beta)-blocker	100–500 μg/kg per min	IV infusion	Very short-acting; constant infusion. May cause bradycardia
Hydralazine <sup>b</sup>	Vasodilator	0.2–0.6 mg/kg per dose	IV bolus or IM	Causes reflex tachycardia, headaches, fluid retention
Labetalol	α(alpha)- and β(beta)-blocker	Bolus: 0.2–1 mg/kg per dose up to 40 mg/dose Infusion: 0.25–3 mg/kg per h	IV infusion or bolus	Use with caution in asthma and heart failure. Preferred in neurologic emergency
Nicardipine	Calcium channel blocker	1–3 μg/kg per min	IV infusion	May cause reflex tachycardia. Preferred in neurologic emergency
Sodium nitroprusside	Vasodilator	0.53–10 μg/kg per min	IV infusion	Associated with cyanide, thiocyanate toxicity. Monitor levels with (>48 h) use or in hepatic or renal dysfunction
Urgencies (severe hypertension with less significant symptoms)				
Clonidine <sup>c</sup>	Central α(alpha)-agonist	0.05–0.1 mg/dose may be repeated up to 0.8 mg total dose	po	Side effects include sedation and dry mouth
Enalaprilat	ACE inhibitor	0.05–0.1 mg/kg per dose up to 1.25 mg/dose	IV bolus	May cause prolonged hypotension, oliguria, and hyperkalemia
Fenoldopam	Dopamine receptor agonist	0.2–0.8 μg/kg per min	IV infusion	Produced modest reduction in BP in a pediatric clinical trial up to age 12 years
Isradipine	Calcium channel blocker	0.05–0.1 mg/kg per dose	po	Stable suspension can be compounded
Minoxidil	Vasodilator	0.1–0.2 mg/kg per dose	po	Most potent oral vasodilator, long-acting

IV indicated intravenous, IM intramuscular, po oral, ACE' angiotensin-converting enzyme, HTN hypertension

<sup>a</sup>Adapted from (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004)

<sup>b</sup>May be used in initial treatment of hypertensive emergency at 0.1 mg/kg dose

<sup>c</sup>Limited reported pediatric experience; smaller doses may be needed in younger children

periods of time (Marik and Varon 2007; Flynn and Tullus 2009).

Labetalol is a combined α (alpha)1- and β (beta)-adrenergic blocking agent. When given intravenously, rather than orally, it may allow for controlled reduction in blood pressure (Goa et al. 1989). The α (alpha)1-blocking effect leads to vasodilatation and reduced peripheral vascular resistance with little effect on cardiac output. Due to its β (beta)-blocking effects, heart rate is usually maintained or slightly reduced. Hypotensive effects of a single dose appear within 2–5 min, peak at 5–15 min, and last up to 2–4 h (Goa et al. 1989). The liver metabolizes the

medication, and elimination is not altered by renal dysfunction. Labetalol is 3–7 times more potent as a β-blocker than α (alpha)-blocker. The beta effects may lead to bronchospasm and bradycardia, and use of labetalol is contraindicated in acute left ventricular failure. It should be used with caution in diabetic patients as it may prevent the signs and symptoms of hypoglycemia. It is recommended for hypertension management in neurologic emergencies such as hypertensive encephalopathy as it does not increase intracranial pressure (Manning et al. 2014; Rivkin et al. 2016). As compared with sodium nitroprusside, systemic and cerebral vascular resistance is

decreased proportionally, maintaining cerebral blood flow to a greater extent with labetalol (Immink et al. 2008). Case series in children have demonstrated its usefulness in the pediatric population (Deal et al. 1992a; Bunchman et al. 1992; Thomas et al. 2011; Lee et al. 2015). Labetalol may be given as a bolus of 0.2–1 mg/kg/dose up to a 40 mg maximum dose or as a continuous infusion of 0.25–3 mg/kg per hour with a maximum 24-h dose of 300 mg (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004; Marik and Varon 2007).

A recent retrospective single-center review of 27 infants and children (age < 24 months) treated for hypertensive crisis or Stage 2 hypertension compared the response to intravenous (IV) infusions of labetalol, nicardipine, or nitroprusside (Thomas et al. 2011). Time to a 20% decrease in systolic BP was similar with all three agents. The authors reported excellent BP reductions with labetalol up to dosages of 0.59 mg/kg/h with little additional benefit at higher dosages suggesting possible dose saturation in this young age group. Immaturities of the glucuronidation pathway of labetalol metabolism or developmental differences in drug distribution were suggested to explain this observation. Reported side effects were similar among agents, although patients receiving labetalol and presenting with ischemic or traumatic brain injury were more likely to develop hypotension requiring discontinuation of the infusion. While acknowledging potential study limitations, the authors suggest caution in initiation of labetalol for severe hypertension in young patients with ischemic or traumatic brain injury (Thomas et al. 2011). Labetalol is, however, a recommended treatment in adult patients with ischemic stroke and severe hypertension (Manning et al. 2014).

Nicardipine, a second-generation dihydropyridine calcium channel blocker, has greater selectivity for vascular smooth muscle than cardiac myocytes. It has strong cerebral and coronary vasodilator activity and minimal inotropic cardiac effects leading to favorable effects on myocardial oxygen balance (Curran et al. 2006). Efficacy in reducing blood pressure was

similar to IV sodium nitroprusside in adults. Nicardipine has comparable safety and efficacy to labetalol in adults, with possibly more predictable and consistent BP control (Peacock et al. 2012). Modest tachycardia may be seen with use of this agent. Onset of action with this medication is rapid within 1–2 min, and duration of action of a single dose is 3 h. Nicardipine undergoes liver metabolism, and the dosage is unaffected by renal dysfunction. Like labetalol, it is recommended for hypertension management in neurologic emergencies such as hypertensive encephalopathy as it does not increase intracranial pressure or ischemic stroke (Manning et al. 2014; Rivkin et al. 2016).

The effectiveness of nicardipine in childhood has been shown in a number of pediatric series involving children as young as age 9 days to age 18 years (Treluyer et al. 1993; Gouyon et al. 1997; Michael et al. 1998; Tenney and Sakarcan 2000; Milou et al. 2000; McBride et al. 2003; Nakagawa et al. 2004; Lee et al. 2015). It has proven to be safe and is generally well tolerated. The recommended pediatric dosage is 1–3 µg/kg per minute (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). Like most other agents, it has not been evaluated by clinical trials in the pediatric population. Reported adverse effects include headache, hypotension, nausea, and vomiting. The manufacturer recommends that IV nicardipine be administered by continuous infusion at a concentration of 0.1 mg/mL. Studies have shown stability when mixed at concentrations of 0.5 mg/mL, thus enabling critically ill patients to be administered smaller volumes of the drug (Baaske et al. 1996). Phlebitis has been reported at the site of administration with higher dosage concentrations (Tenney and Sakarcan 2000), suggesting the medication should in this situation be given through a central line. Elevated tacrolimus levels have been reported in pediatric renal transplant recipients receiving nicardipine (Hooper et al. 2011).

Hydralazine is a direct vasodilator of arteriolar smooth muscle. The mechanism of action is unclear, although it may involve alterations in intracellular calcium metabolism (Thomas 2011). Hydralazine-induced vasodilatation leads to stimulation of the

sympathetic nervous system resulting in tachycardia, increased renin release, and fluid retention. The onset of action is within 5–30 min after intravenous administration. Average maximum decrease in blood pressure occurs 10–80 min after intravenous administration (Flynn and Tullus 2009). This medication can be given intramuscularly. The recommended dosage for pediatric patients is 0.1–0.6 mg/kg per dose given intravenously every 4–6 h (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). Given as a bolus rather than continuous intravenous medication, hydralazine may be more useful in individuals with hypertensive urgency that are unable to tolerate oral medications than in a hypertensive emergency. Two recent reports have reviewed the use of this medication in hospitalized children and adolescents. Median reduction of systolic and diastolic blood pressure was 8.5% and 11.5%, respectively, in one report (Ostrye et al. 2014), and mean BP reduction was 19% in the other (Flynn et al. 2016). While nearly half of patients achieved an ideal clinical response of 10–25% BP reduction within 6 h of administration, response was variable with 31% having an excess reduction of >25% in BP though few adverse events were reported (Flynn et al. 2016).

Esmolol is an ultrashort-acting cardioselective  $\beta$  (beta)-blocking agent. Onset of action with this medication is within 60 s with offset of action in 10–20 min. Metabolism of this agent is by rapid hydrolysis of ester linkages by RBC esterases and is not dependent on hepatic or renal function. Pharmacokinetics of this agent in children did not differ from adults (Adamson et al. 2006; Tabbutt et al. 2008). A trial in children with coarctation of the aorta included 116 patients less than age 6 years who received esmolol at low (125  $\mu\text{g}/\text{kg}$ ), medium (250  $\mu\text{g}/\text{kg}$ ), or high dose (500  $\mu\text{g}/\text{kg}$ ). Systolic blood pressure decreased significantly from baseline on average by 6–12.2 mmHg by group but failed to show a dose-response relationship. Heart rate reduction ranged 7.4–13.2 beats per minute by group, and no serious adverse events occurred (Tabbutt et al. 2008). Pediatric studies with this agent in non-cardiac conditions have not been reported.

Fenoldopam is a dopamine D1 receptor agonist that does not act at D2 receptors. This leads to vasodilatation of renal, coronary, and cerebral arteries as well as peripheral vasodilatation. Onset of action is within 5 min with 50% of the maximal blood pressure-lowering effect occurring within 15 min and maximal effect by 1 h. The duration of action after stopping the medication is 30–60 min. This medication has been effective in reducing blood pressure in adults with hypertensive emergencies where it has proven to be as effective as nitroprusside (Murphy et al. 2001; Marik and Varon 2007). It has also been used as a renal protective drug in critically ill adult and pediatric patients (Murphy et al. 2001; Moffett et al. 2008). One pediatric trial conducted in 77 children aged 1 month to 12 years undergoing controlled hypotension during surgery compared response to one of four doses of fenoldopam (0.05, 0.2, 0.8, or 3.2  $\mu\text{g}/\text{kg}$  per minute) (Hammer et al. 2008). Dosages of 0.8 and 3.2  $\mu\text{g}/\text{kg}$  per minute significantly decreased blood pressure but resulted in increases in heart rate of 9–17 beats per minute. The effective dose range appeared to be higher (0.8–1.2  $\mu\text{g}/\text{kg}$  per min) than as labeled for adults (0.05–0.3  $\mu\text{g}/\text{kg}$  per min). Only a single case report of use of this agent for a hypertensive emergency in childhood has been reported (Lechner et al. 2005).

Enalaprilat, an intravenous angiotensin-converting enzyme (ACE) inhibitor, produces vasodilatation and decreases peripheral vascular resistance. Onset of action is 30–60 min and duration of action 4–6 h. Elimination is primarily renal, and dosage adjustment is needed if the patient has renal impairment. Blood pressure reduction is variable, and hypotension may occur more often in high renin states (Marik and Varon 2007). One pediatric case series in 10 premature neonates receiving doses of 7.4–22.9  $\mu\text{g}/\text{kg}$  per 24 h demonstrated a reduction in mean arterial pressure within 30 min of enalaprilat administration that persisted generally for a median of 12 h (Wells et al. 1990). Side effects included hypotension, oliguria, elevated serum creatinine, and transient hyperkalemia in some infants. Given the higher baseline plasma renin activity, and incidence of renovascular hypertension in childhood,

this medication is infrequently used in the pediatric age group.

Clevidipine is a new, third-generation calcium channel blocking agent approved for use in adults with severe hypertension. This medication inhibits L-type calcium channels, thus relaxing vascular smooth muscle in small arteries resulting in a reduction of peripheral vascular resistance. Onset of action is 2–4 min with offset of effect in 5–15 min. Like esmolol, this medication is rapidly metabolized by RBC esterases and not affected by hepatic or renal function (Deeks et al. 2009). Clevidipine by continuous infusion effectively reduced BP in adult cardiac surgery patients and was more effective at maintaining systolic BP within preset target limits than intravenous nitroglycerin or nitroprusside in preoperative patients. It was as effective as nicardipine in the postoperative setting. In adults with acute severe hypertension, clevidipine lowered blood pressure in most patients (88.9%) to the prescribed target within 30 min of initiation of treatment (Pollack et al. 2009). Limited experience has been reported for perioperative management of hypertension in children with this agent (Tobias et al. 2013).

Clonidine is a centrally acting  $\alpha$  (alpha)-2-adrenergic agonist, which decreases cerebral sympathetic outflow. Its onset of action is 30–60 min after administration and duration 6–8 h. It should be avoided in patients with altered mental status because of its common side effect of drowsiness. Other complications of this therapy may include dry mouth, occasional dizziness, and the development of hypertensive crisis upon abrupt discontinuation of therapy (Geyskes et al. 1979). Oral clonidine loading in adults utilizes an initial dosage of 0.1–0.2 mg followed by hourly dosages of 0.05–0.1 mg until goal BP is achieved or a total of 0.7 mg has been given. This approach to treatment of severe hypertension is reported to be successful at reaching target BP in 93% of adult patients (Houston 1986). Hypotension occurred more often in volume-depleted patients. Average total dose requirements have ranged in studies from 0.26 to 0.45 mg. While published reports of clonidine treatment in childhood are limited to chronic oral or transdermal therapy in adolescents (Falkner et al. 1983, 1985), suggested dosages for

severe hypertension in children have been given (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004).

Isradipine is a second-generation dihydropyridine calcium channel blocker, which acts selectively on L-type channels on vascular smooth muscle but not myocardial cells. Because it does not affect myocardial contractility, it can be used in patients with decreased myocardial function (Sahney 2006). Onset of action is by 1 h with peak effect at 2–3 h when administered orally (Flynn and Pasko 2000). Medication half-life is 3–8 h. A stable extemporaneous suspension of isradipine may be compounded for use in small children (MacDonald et al. 1994). Several pediatric series of the use of this medication for management of hypertension have been reported (Johnson et al. 1997; Strauser et al. 2000; Flynn and Warnick 2002; Miyashita et al. 2010). A recent report in 282 children with acute hypertension receiving isradipine demonstrated a median decrease in systolic BP of 16.3% and diastolic BP of 24.2%. The greatest decrease in BP was observed in children below age 2 years where the authors suggest a lower initial dosage of 0.05 mg/kg be utilized. Higher dosages were associated with more frequent drops in mean arterial pressure > 25%. The most common adverse effects included vomiting, nausea, and headache (Miyashita et al. 2010).

Minoxidil, an oral antihypertensive, is metabolized to minoxidil sulfate, which opens K<sup>+</sup> channels in vascular smooth muscle cells permitting K<sup>+</sup> efflux, hyperpolarization, and relaxation of smooth muscle. This produces arteriolar vasodilatation and a reduction in BP and peripheral vascular resistance. Peak concentrations of minoxidil occur 1 h after oral administration, though the peak antihypertensive effect is later, possibly due to delayed formation of the active metabolite. Duration of action may be up to 24 h. Tachycardia may develop with minoxidil use as well as salt and water retention (Thomas 2011). Reported use in childhood includes severe chronic hypertension refractory to other medications and for acute BP elevations in children with chronic hypertension (Pennisi et al. 1977; Strife et al. 1986).

## Conclusion

Severe, symptomatic hypertension requires immediate evaluation and rapid institution of anti-hypertensive therapy. Use of continuous infusions is recommended to allow BP reduction in a controlled manner, avoiding overly aggressive therapy that may also lead to ischemia and further injury. A number of medications are available, although much remains to be learned about optimal treatment of this condition in childhood.

## Cross-References

- ▶ [Diagnostic Evaluation of Pediatric Hypertension](#)
- ▶ [Methodology of Casual Blood Pressure Measurement](#)
- ▶ [Neurohumoral and Autonomic Regulation of Blood Pressure](#)
- ▶ [Secondary Forms of Hypertension in Children: Overview](#)
- ▶ [Sequelae of Hypertension in Children and Adolescents](#)

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**Part V**

**Hypertension Research in Pediatrics**

Julie R. Ingelfinger

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## Abstract

Much of what we know about the physiology of blood pressure (BP) regulation and the pathogenesis and treatment of human hypertension has been derived from studies in other animal species. This chapter presents a variety of models of experimental hypertension with the intent of providing a background for the interested reader. Many models explore normal and abnormal physiology without genetic manipulation but rather with the use of surgery, infusion of medications, alterations in diet, and application of stressful conditions. In other models, inbreeding or genetic manipulation is used to produce increased (or decreased) BP. The many models available should be considered both for carrying out research and for evaluating published studies.

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## Keywords

Experimental hypertension • Animal models • Transgenic • Knockout • Renovascular hypertension • Consomic • Congenic

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## Introduction

The understanding of human hypertension has been accelerated by the development of a number of experimental animal models. Ever since the early 1700s, when the Reverend Stephen Hales (Hales 1733; Felts 1977) measured blood pressure (BP) in a horse by inserting a brass cannula into an artery and observing the height of the blood in a glass extension tube, experimental models have been important for the study of BP, hypertension, cardiovascular disease, and kidney disease. Presently, there are a variety of such models – models that explore normal and abnormal physiology and models in which inbreeding or genetic manipulation has increased or decreased BP.

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There is wide agreement that the best experimental models for the study of human disease should mimic the entity in question in people – both in the anatomy, physiology and disease course. Thus, the most useful experimental models should facilitate studies both as the disease evolves and in stable, chronic disease. Further, a useful animal model must adhere to current animal welfare regulations and needs to be technically feasible and financially supportable. This chapter will review some of these models with the intent of providing a resource for the interested reader.

## Non-genetic Models of Hypertension

Non-genetic models of hypertension utilize either infusion of drugs or substances, dietary manipulation or surgical procedures to produce hypertension (Table 1). Depending upon the research focus, one or another of these models may be useful.

**Table 1** Models of hypertension without genetic modification

Surgically induced models of hypertension	
1. Renal artery stenosis	
2 kidney, 1 clip	
1 kidney, 1 clip	
intra-renal aortic clip	
2. Wrapped kidney-Page kidney	
3. Coarctation of the aorta	
Pharmacologic models of hypertension	
1. Angiotensin II infusion	
2. DOCA administration	
3. Infusion of other pressors, e.g., endothelin	
4. Blockade of relaxing factors, e.g., NO via L-NAME	
Dietary models of hypertension	
1. High salt diet	
2. High fructose diet	
Stress-induced hypertension	
1. Noise	
2. Circadian disruption	
3. Cold or heat	
4. Electric stimulation	

DOCA, deoxycorticosterone acetate; NO, Nitric oxide; L-NAME

## Induction of Hypertension with Substances and Drugs

Tigerstedt and Bergman, whose work constitutes the underpinning of much of cardiorenal physiology, discovered renin and demonstrated in 1898 that the infusion of a crude preparation of rabbit kidney extract increased BP markedly (Tigerstedt and Bergman 1898). They hypothesized that “a blood-pressure raising substance is made in the kidneys and passed into the blood,” and they coined the name “renin.” However, their experiments on the infusions of kidney extract attracted minimal notice until several decades later, when the importance of renovascular hypertension was discovered in the 1930s (Goldblatt et al. 1934). Intense research on hypertension from the 1930s onwards has resulted in a large body of knowledge about the renin-angiotensin-aldosterone system ((RAAS), see “► Vasoactive Factors and Blood Pressure in Children”). It is now well appreciated that infusion of angiotensin II (Ang II), depending upon the dose, rate, and duration, can increase BP acutely, gradually, and chronically (Carroll et al. 1987; Dornas and Silva 2011; Guild et al. 2012; McCubbin et al. 1965; Moon 2013). In addition, many studies have been done using agents that block or interfere with the RAAS at key steps in the cascade. The step at which the RAAS is blocked can be used to probe the role of a given component of the RAAS.

A model that has been commonly used for three-quarters of a century is induced by administration of deoxycorticosterone acetate (DOCA) and excess sodium chloride (generally as 0.9% saline in drinking water), often following uninephrectomy (Selye 1942). The resultant low-renin model of hypertension contrasts with the surgically induced and angiotensin-II infusion high-renin hypertension models. Central nervous system mechanisms are important in maintaining this form of hypertension (Katholi et al. 1980; Mohring et al. 1977).

Additional hormonal systems also affect BP and are used to develop animal models for study. Among there are endothelins, Nitric oxide (NO) and its metabolites, catecholamines, and natriuretic peptides. Nitric oxide is a key substance in controlling peripheral vascular resistance via its

vasodilatory effects (Török 2008). The inhibition of NO synthase with L-NG-nitroarginine methyl ester (L-NAME), for example, results in hypertension that is accompanied by marked peripheral vasoconstriction (Baylis et al. 1992; Ribiero et al. 1992). Endothelin is a potent vasoconstrictor molecule – more potent than either Ang II or epinephrine. The renal vasculature, in particular, is sensitive to endothelin 1 (ET-1). Administered ET-1 constricts both afferent and efferent arterioles, so it decreases GFR and renal blood flow (Abassi et al. 2001; Inscho et al. 2005; Shreenivas and Oparil 2007). In certain regions of the kidney, for example, in the medulla, ET-1 can lead to NO-dependent vasodilation. The main lesson from all of these infusion models is that one can gain substantial knowledge about the effects of vasoactive substances on BP; additional vasoactive substances may well be discovered, and infusion studies are helpful in learning more about each such substance.

## **Surgically Induced Models of Hypertension**

### **Surgically Induced Renovascular Hypertension**

A breakthrough in the understanding of the role of the kidney in hypertension was made by Dr. Harry Goldblatt, a major innovator who created important animal models of renovascular hypertension (Goldblatt et al. 1934). He pioneered the first experimental model of hypertension, having observed that constriction of one renal artery in dogs led to severe hypertension (widely called the 2 kidney, 1 clip model) (Goldblatt et al. 1934). When partial vascular obstruction is induced by placing a clip on the artery to one kidney, the perfusion pressure to that kidney decreases; the decreased perfusion pressure ultimately increases both the synthesis of renin and Ang II, which leads to increased total peripheral resistance and systemic hypertension. There are several anatomic variations of this renovascular model of hypertension – using clips on both renal arteries (2 kidney, 2 clip) or using one clip and removing the contralateral kidney (1 kidney,

1 clip model, or 1K, 1C). In the 1 kidney, 1 clip model, the normal contralateral kidney has been ablated, and thus, there is no contralateral kidney to compensate for the salt and water retention on the clipped side. Thus, the 1 kidney, 1 clip model has been used to study salt and water retention in hypertension (Wiesel et al. 1997). Additionally, placement of a surgical clip on the aorta between the two kidneys produces hypertension as well and has also been used as a model of hypertension (Pinto et al. 1998).

The 2 kidney, 1 clip model was expanded to other animal species within a decade of its first description; many variants have been reported since (Fuji et al. 1967; Leenen and de Jong 1971; Lerman et al. 1999; Panek et al. 1991; Pickering and Prinzmetal 1937; Romero et al. 1981; Wiesel et al. 1997). In dogs, the 2K, 1 clip model produces elevations in BP over several days, and the BP level plateaus thereafter. However, between 10% and 20% of the animals spontaneously have a decrease in their BP with time, likely because the dog often develops collateral vessels to the kidney. In contrast, the hypertension with the 2K, 1 clip model is generally more severe in the rat.

### **Hypertension from Perinephric Compression**

In 1939, Irwin Page developed a model of hypertension in the dog in which perinephric renal pressure was increased by simply wrapping one kidney with cellophane (often called the “Page kidney”) (Page 1939). This maneuver, in turn, leads to parenchymal compression. In humans, hypertension from renal parenchymal compression is rare but occasionally occurs due to the presence of a subcapsular hematoma or subcapsular fluid, or some other process such as retroperitoneal fibrosis that creates sufficient perinephric pressure to impede renal blood flow. For example, a recent short report detailed the case of a child with a solitary kidney who developed a Page kidney after a tobogganing accident that involved blunt renal trauma (Tuong et al. 2016). Such hypertension may be severe, accompanied by increased activity of the RAAS, loss of kidney function, and features of secondary aldosteronism.

### Subtotal Nephrectomy and Renoprival Hypertension

Subtotal nephrectomy often results in hypertension (Blantz and Gabbai 1989; Greene and Sapirstein 1952; Hayslett 1979). In a model in which one kidney is removed as well as two-thirds of the remaining kidney (subtotal nephrectomy – five-sixths of the total renal mass), the hypertension that ensues is often accompanied by increased intravascular volume. The features of subacute nephrectomy hypertension are influenced by how long the animal is followed, as well by the diet allowed after the procedure, and whether the adrenal glands are left intact. Some animals subjected to subtotal nephrectomy develop secondary focal segmental glomerulosclerosis (FSGS) with the markedly reduced renal mass, which itself may further impact the BP.

Anephric patients on dialysis may experience hypertension, but experimental models of renoprival hypertension are challenging, as maintaining such a model may be difficult without embarking on chronic dialysis of the animal (Ferrario et al. 2009).

### Neurogenic Hypertension

The central nervous system modulates BP and can be involved in the production of hypertension (Barnes et al. 1977; Ferrario et al. 2009; Krieger 1967). A number of denervation techniques have been employed to investigate central mechanisms of neurogenic hypertension. Sinoaortic baroreceptor denervation is the most commonly used method and results in predictable hypertension (Krieger 1967). The technique was first reported by Krieger in 1967 (Krieger 1967) and leads to increased intravascular volume and increased peripheral vascular resistance.

### Dietary Models of Hypertension

Prolonged exposure to high-salt, high-fat, or high-sugar diet may lead to increases in BP (Chapman and Gibbons 1950; Dornas and Silva 2011; Haddy 2006). The mechanisms by which this occurs are incompletely understood, but dietary models are

presently very important, given the high prevalence of both obesity and intake of fast food. Very high salt intake decreases plasma NO and decreases urinary nitrate excretion, while increasing superoxide (Roberts et al. 2000, 2003). Clinical hypertension may be salt sensitive (Hollenberg 2006), and high salt intake in some strains of animals leads to hypertension, as in the Dahl salt-sensitive rat strain (Dahl et al. 1968). The ingestion of increased fructose in the diet also leads to hypertension in animals. Studies starting in the 1980s suggested that Sprague-Dawley and Wistar-Kyoto rats develop hypertension as well as insulin resistance when fed a diet high in fructose (Ehrlich and Rosenthal 1995; Hwang et al. 1987). However, the same diet in other species, such as the dog, does not lead to hypertension. There is currently substantial interest in the role of fructose in hypertension and cardiovascular disease (Johnson et al. 2007).

### Models of Stress-Related Hypertension

A number of stress-related animal models of hypertension have been developed. These generally involve aversive stimuli such as unpleasant noise, restraining cages, extreme temperatures (hot or cold), or flashing lights (Bechtold et al. 2009; Henry et al. 1993; Münzel et al. 2017).

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### Genetic Forms of Hypertension

#### Inbred Strains and the Development of Hypertension

The use of inbred rat strains for the study of hypertension has been common for over 50 years (Bianchi et al. 1974; Dahl et al. 1962; Heller et al. 1993; Kuijpers and Gruys 1984; Markel 1992, 1995; Okamoto and Aoki 1963; Okamoto et al. 1986; Rapp 2000; Smirk and Hall 1958; Vincent et al. 1978; Zamir et al. 1978). The development of hypertension in such models is of special interest to investigators who have an interest in hypertension in the young, since the animals usually develop hypertension as they mature. In 1958, Smirk and Hall published



a report about a strain of New Zealand rats that had increased BP (Smirk and Hall 1958). A few years later, the development of the spontaneously hypertensive rat (SHR) was reported (Okamoto and Aoki 1963). There are multiple other rat strains associated with hypertension – the Dahl salt-sensitive rat and salt-resistant rat strains (Dahl et al. 1962), the Milan strain (Dahl et al. 1962), the Sabra strain (Zamir et al. 1978), and the Lyon (Vincent et al. 1978) strain. A stroke-prone strain has been developed from the SHR strain (Okamoto et al. 1986). A list of inbred rat strains may be found in Table 2.

To create a relevant strain to study a given disease, animals with the phenotype of interest are bred selectively for several generations (reviewed in Lerman et al. 2005). Once the trait appears reliably, sib-mating is performed for roughly 20 generations so that there is genetic homogeneity. The SHR and the stroke-prone SHR were created using this approach. That being said, the SHR is not completely inbred, and substrains vary in expression of a number of traits.

A further refinement of inbreeding strains is the use of congenic and consomic strains (Cowley et al. 2004; Nadeau et al. 2000; Singer et al. 2004;

**Table 2** Well-characterized rat models of genetic hypertension

Rat strain	Phenotype	Control strain	Background	Reference
<b>RAT-breeding</b>				
Spontaneously hypertensive rat (SHR)	Hypertensive by age 4 weeks	Wistar-Kyoto (WKY)	Wistar	Okamoto and Aoki (1963)
Stroke-prone SHR	Bred from SHR; prone to stroke		SHR	Okamoto et al. (1986)
Dahl salt-sensitive	Hypertension with salt loading	Dahl salt-resistant	Sprague-Dawley	Dahl et al. (1962)
Milan hypertensive (MHS)	Bred as model for studying cation transport	Milan normotensive (MNS)	Wistar	Bianchi et al. (1974)
New Zealand genetically hypertensive		Controls generally unselected	Wistar	Smirk and Hall (1958)
Sabra hypertensive (SBH)		Sabra normotensive (SBN)	Unknown/unclear	Zamir et al. (1978)
Lyon hypertensive rat	Low-renin hypertension	Lyon normotensive and Lyon low BP	Sprague-Dawley	Markel (1992)
Fawn-hooded hypertensive rat	Hypertension, kidney disease, and platelet abnormalities		German brown × white Lashley	Kuijpers and Gruys (1984)
Prague hypertensive rat		Low BP Prague strain	Wistar	Heller et al. (1993)
Russian inherited stress-induced arterial hypertensive rats (ISIAH)	Stress-induced hypertension		Wistar	Markel (1995)
<b>Rat-transgenic</b>				
Renin-mediated	Mouse Ren-2 gene inserted into rat			Chung et al. (1993), Pinto et al. (1998)

A transgenic model can be generated by overexpression of a specific gene, for example, the mouse Ren-2 gene and TGR (mREN2)27 (Mullins et al. 1990). Manifestations include marked cardiac hypertrophy, moderate proteinuria, and impaired endothelium-dependent relaxation (Kimura et al. 1992; Yang and Sigmund 1998)

Yagil et al. 2003) in which the resultant animals differ only by a single gene or single chromosome. Development of such animals is particularly useful in studying complex traits such as hypertension.

A congenic rat or mouse is created by mating animals from an inbred strain that carry one foreign gene and continuing such mating until the congenic strain and the inbred strain are identical, except for the transferred locus and the chromosomal segment to which it is linked. In other words, one breeds the first generation offspring with the parental generation (a backcross). The animals picked each time to breed are selected with the use of markers. When relevant quantitative trait loci (QTL) have been identified via genome-wide scanning, breeding animals that differ only in a given QTL facilitates the study of the implicated chromosomal regions. It generally takes ten generations of backcrosses to attain a congenic strain.

For example, Flister et al. (2012) used a series of congenic rat lines that transferred part of the salt sensitive (SS) Dahl rat chromosome 12 into the Brown Norway consomic rat to hone in on several BP loci of interest. They found that transferring a 6.1 Mb portion of SS chromosome 12 confers salt-sensitive hypertension.

When an entire chromosome is exchanged by a homologous chromosome from another strain, the strain is called consomic. This is accomplished by creating an inbred strain that has one single chromosome that differs by being replaced using serial backcrosses that are marker assisted. Thus, the resultant animal is fully inbred and has one intact pair of homologous chromosomes from an inbred donor strain. Given that, the effect of a specific chromosome that differs can be compared to an inbred group of animals who do not have the donor chromosome, but their native chromosome. Such animals are very helpful for targeted screening to detect recessive mutations that have quantitative effects.

## Sexual Dimorphism Models

A number of the phenotypically bred models of hypertension exhibit sexual dimorphism and thus

lend themselves to the study of differential expression in males and females (Ellison et al. 1989; Fortepiani et al. 2003a, b; Reckelhoff and Granger 1999). For example, hypertension and cardiovascular disease are more pronounced in male SHR (Ellison et al. 1989; Reckelhoff and Granger 1999). In the Sabra rat, there appear to be QTLs (quantitative trait loci) for salt sensitivity expressed on chromosome 1 that differ by gender (Yagil et al. 2003). These are SS1a and SS1b in male rats but only SS1b in females.

## Murine Models of Mendelian Hypertension

### Mendelian Models

The resorption of salt and water by the kidney importantly regulates BP, and a number of murine models have been developed to study both hypertension and hypotension. For example, a murine model of Liddle syndrome, which is caused by a gain-of-function mutation in the epithelial sodium cotransporter (ENaC) gene, was created by the introduction of a stop codon into the mouse ENaC locus (Pradervand et al. 1999). That particular mouse model has many of the features of the human disease. Similarly, there are models of other rare Mendelian forms of hypertension such as Gordon's syndrome (reviewed by Chen and Coffman (2012)).

### Transgenic, Knock Out, and Knock In Models

The role of the RAAS and other hormonal systems in hypertension has been extensively studied with the use of transgenic, knock out, and knock in models (Billet et al. 2007; Chen and Coffman 2012; Kimura et al. 1992; Mullins et al. 1990; Thompson et al. 1995; Yang and Sigmund 1998). Transgenic animals contain exogenous genetic information that is inserted into its genome stably and can be passed on to additional generations. The inserted transgene permits the investigation of the role of cis- and trans-acting factors that control gene expression. Most transgenic animals are mice, though an important model is the TFR (mREN2) 27 transgenic rat

that was developed by John Mullins and colleagues (Mullins et al. 1990). Fulminant hypertension develops in this animal early in life. Knock out animals have a given gene ablated, while knock in animals contain additional copies of a gene of interest.

A variety of transgenic, knock out, and knock in animals have been developed that have been used in studying hypertension. For example, mice transgenic for the rat angiotensinogen gene become hypertensive (Kimura et al. 1992). There are also mouse transgenic for renin (Sigmund 1993) and other components of the RAAS (reviewed in Cvetkovic and Sigmund 2000; and Chen and Coffman 2012). It is also possible to use an animal in which a gene has been ablated and selectively replace it in only one organ at a time (Kessler et al. 2005). For example, Kessler et al. ablated ACE in a mouse model and then selectively targeted the ACE gene to the vasculature, the testis, or the kidney, permitting the study of the effects of the gene when present in specific regions of the body. The number of such animal models is constantly increasing, and as new methods for targeting specific organs or cells within organs progress, it is possible to ask very specific questions that get at the mechanism of hypertension.

### Tissue and Organ Manipulation

The many techniques now available make it possible to increase local gene expression or to silence it. Using a lentiviral construct containing heme oxygenase, Cao and colleagues (2011) targeted vascular endothelium, which ameliorated vascular function in an angiotensin II model of hypertension in the rat. In another approach, Sriramula et al. increased the expression of ACE2 in the paraventricular nucleus, which decreased hypertension induced by Ang II infusion. In that setting, the expression of ACE and the AT1 receptor decreased, while the AT2 receptor and Mas expression increased. Further the increased expression of ACE2 decreased pro-inflammatory cytokines (Sriramula et al. 2011).

Decreasing expression of a gene may be helpful in other models; using silencing technique, Zhu et al. decreased the expression of the *HIF*

*prolyl-hydroxylase 2* gene in the renal medulla, which attenuated salt-sensitive hypertension in the Dahl S rat (Zhu et al. 2014).

### In Vitro Models of Hypertension

There are many unique approaches to the study of hypertension that involve in vitro experiments (reviewed in Cook and Re 2012). Use of tissues from any of the above models is a common way to assess the damage from hypertension. In addition, isolating cells from pharmacologically treated animals or from genetically modified animals and placing them into primary culture allows studies of cellular and subcellular aspects of hypertension. Custom arrays are being developed in order to be able to assess and compare different animal models of hypertension in vitro (Northcott et al. 2012).

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### Conclusions

The choice of an appropriate model of hypertension depends on the research question one wishes to study (Sarikonda et al. 2009). The present chapter is far from exhaustive but is meant to indicate that with the many techniques available, investigators can design specific models to perform mechanistic studies that may inform pathogenesis, which may lead to new targets for the treatment of hypertension. It is hoped that this brief outline of some of the available models and concepts underlying their development may be a starting point for the reader's consideration.

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### Cross-References

- ▶ [Insulin Resistance and Other Mechanisms of Obesity Hypertension](#)
- ▶ [Monogenic and Polygenic Contributions to Hypertension](#)
- ▶ [Stress and Salt Sensitivity in Childhood Hypertension](#)
- ▶ [Vasoactive Factors and Blood Pressure in Children](#)

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# Cohort Studies, Meta-analyses, and Clinical Trials in Childhood Hypertension

# 47

Nicholas Larkins and Jonathan Craig

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## Abstract

Clinical research involving children with hypertension poses unique opportunities and challenges. In particular, the complications of hypertension accrue over the course of many years and are relatively infrequent, so studies need to be large and long term to identify clinically important end points. Despite the challenges, an evidence base is beginning to amass that should eventually answer many of the relevant questions. We now have a good idea of how blood pressure tracks from the beginnings of life to early adulthood and an understanding of the relative importance of different risk factors. This chapter aims to inform the reader of different study designs as they apply to pediatric hypertension, and how these can be applied to answer specific questions of clinical importance. We also discuss the strengths and weaknesses of different study designs, and the results of some particularly impactful trials are discussed. Recent advances in study design and epidemiology are covered, with a focus on the potential role of data sharing.

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## Keywords

Research design • Epidemiology • Blood pressure

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## Introduction

Clinical studies allow us to translate discoveries in basic science to patient-level care. Broadly speaking, these consist of observational and interventional studies. Through the observation of risk and outcomes in patients, we gain insights into the prevalence and mechanisms of disease. We then attempt to apply this understanding to improve patient care through interventional trials, which in their most robust form include the randomization of participants. The resulting body of evidence can then be further analyzed through systematic review and meta-analysis to provide an unbiased overview for clinicians and patients.

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Children with hypertension stand to benefit from clinical research in the same way as any other patient group. However, children with hypertension from an early age will have a greater cumulative exposure than older people and so are at increased risk of sequelae (Rapsomaniki et al. 2014). In addition, it would seem plausible that early intervention for hypertension-related disease might lead to better long-term outcomes, although this hypothesis would be difficult to test formally. These observations, in combination with the relative importance of hypertension as an attributable and modifiable risk factor for chronic disease with a global impact, give us impetus to pursue research in this field (Lim et al. 2012).

In this chapter, rather than describe individual studies in depth, we will discuss the role and design of notable studies that have improved the care of children with hypertension. This will be done in the context of discussion around different types of study design (Table 1). We hope that this chapter will enable readers to understand the strengths and limitations of different approaches to clinical research in children, with particular application to childhood hypertension (Table 2).

## Cross-Sectional Studies

Cross-sectional studies are used to examine a population at one particular moment in time. The data derived from cross-sectional studies can inform us in three primary ways. Firstly, cross-sectional data are useful in determining the prevalence of disease

and its risk factors, that is, the proportion of the population who have a disease at one point in time and the proportion who have putative factors. Given there is no component of time, incidence, which is the rate of new events over a finite time, cannot be calculated. Second, cross-sectional data can also be used to generate hypotheses through the exploration of relationships between outcomes and potential explanatory (causative) variables. This information can then be expanded upon, and causal relationships tested, in future prospective studies. Finally, cross-sectional data can be used to investigate the accuracy of diagnostic tests and their performance in clinical practice.

## Strengths and Weaknesses

Cross-sectional studies are a common study design because they are easy to perform and often impose little additional burden on patients or clinicians beyond routine clinical care. A well-performed cross-sectional study will answer a specific clinical question that does not require ongoing patient follow-up. For example, how common is hypertension in children, can we identify subgroups with an increased prevalence of hypertension, or what is the accuracy of a new method of measuring blood pressure (BP)?

The most important limitation of a cross-sectional study design is the inability to move beyond correlation and explore causation. This means that while observed relationships might be of interest in the context of other data or in generating new hypotheses, they are usually not sufficient in themselves to impact patient care.

**Table 1** Study designs

	Advantages	Disadvantages
Cross sectional	Cheap and easy to run	Unable to determine causality
	Provide important information on prevalence of disease and risk factors	
	Used in studies of diagnostic test accuracy	
Cohort	Can suggest causal relationships where temporal associations are present	Less confounding than cross sectional but cannot exclude entirely
	Used to determine the prognosis	
Randomized control trial	Can determine causality in the presence of unmeasured confounders	Expensive and logistically demanding May have limited translation
Systematic review	An unbiased summary of evidence	Limited by quality and availability of primary evidence



**Table 2** Key elements of critical appraisal for different study designs

All studies	Is there sufficient information to assess the validity of the results (use of accepted reporting criteria)?
	Have multiple comparison been performed, and if so are the results appropriately labelled as hypothesis generating?
	Are the results generalizable to the children I care for?
Cross sectional	Were the estimates adequately adjusted for confounding?
	Are the conclusions justified within the limitations of the data and study design?
Diagnostic test accuracy	Was the place of the test in the diagnostic pathway clear?
	Was an appropriate spectrum of patients enrolled?
	Was the reference test chosen valid and applied to all patients?
	Were intermediate and ambiguous test results included?
Cohort	How many and which participants were lost to follow-up?
	How was the resultant missing data handled?
	Are the methods of analysis appropriate for the data gathered (e.g., were methods of correlated data analysis applied to repeating measures)?
Randomized controlled trial	Was the randomization sequence truly random?
	Has the allocation sequence been adequately concealed?
	What groups involved in the study were blinded, and how was this done?
	Does the final analysis reflect the initial study protocol?
	Was the primary outcome patient relevant and measured appropriately?
	Has an intention-to-treat analysis been performed?
Systematic review	Was the search strategy broad and reproducible?
	Were the inclusion and exclusion criteria appropriate for the question being asked?
	What was the quality of included trials, and could this have introduced bias?
	Was there a thorough examination of heterogeneity, and how this might affect the validity of summary estimate?
	Is publication bias likely?

## How to Read

Normally, in the conduct of a cross-sectional study, only a relatively small proportion of the total population of interest is sampled. When the study population is a representative of the general population, we can then extrapolate the findings to make predictions about the general population. It is usual to provide a statistical measure of the uncertainty surrounding the point estimates (e.g., the prevalence of a given disease), as expressed as by the 95% confidence interval (CI). That is, the range in which we can be 95% confident the true population point estimate lies.

In addition to a presentation of the uncertainty surrounding the estimates provided, readers should expect to see some adjustment for confounding. This is normally accomplished through multivariable analyses where the relationship between the predictor of interest and outcome is adjusted for other predictor variables that are

also known to affect the outcome measure. A loss of statistical power will occur in this process (reflected in a widening of the confidence intervals), which can be a problem in smaller studies. However, what we are mostly looking for is a clinically relevant difference between the adjusted and unadjusted estimates, in which case confounding is present, and the unadjusted estimates may be misleading.

By using these principles, a reliable cross-sectional study will produce reliable estimates of prevalence or information about association between variables that can be translated into future research. When reading a cross-sectional study that focuses on associations, the authors should be expected to place the research into the context of the broader scientific literature and proposed future research.

*The perils of p-values:* The analysis of data normally also involves the testing of hypotheses

against the null hypothesis, the presumption that no relationship exists. In a similar way that the variance of the data and sample size can be used to calculate confidence intervals, a  $p$ -value can be calculated that represents the probability that an observed estimate differs from the null hypothesis by chance alone. While the  $p$ -value is a useful piece of information when interpreting the results of statistical analyses, it is prone to errors in application and often misinterpreted (Altman 2000).

Firstly, the  $p$ -value is not valid unless the correct statistical test is used. All tests are based on a number of underlying assumptions, and authors need to demonstrate that these have not been violated in the analysis. As computer packages and databases become more approachable, it is easier for people with a limited understanding of statistics to produce and publish the results of hypothesis testing that are not valid (Grimes and Schulz 2012).

Typically, a two-sided  $p$ -value of 0.05 is used to denote significance. This information can normally also be gleaned from the 95% confidence interval. If the confidence interval does not include the null hypothesis, then the  $p$ -value is less than 0.05. When presented as a continuous value (rather than simply less than or greater than 0.05), a  $p$ -value can be useful in representing more precisely how certain we can be of refuting to the null hypothesis.

The  $p$ -value normally assumes that a relationship is tested only once. If the same relationship is tested multiple times, the results of standard hypothesis testing are no longer valid. A common situation, particularly in cross-sectional data analyses, is for the same or very similar hypotheses to be tested multiple times, and only the significant  $p$ -values are to be reported. This problem is one of multiplicity. There are statistical techniques to adjust  $p$ -values for multiple comparisons (Schulz and Grimes 2005). However, their application is controversial, as the resultant  $p$ -values no longer represent a singular hypothesis test and so can be difficult to interpret (Rothman 1990). Adjustments for multiplicity do not take into account the differing amount to which groups of tests performed could have a plausible biological relationship. Thus, the unadjusted results are

normally presented, and readers must interpret the  $p$ -value in the context of the other results.

Finally, regarding hypothesis testing and  $p$ -values, the two key domains for decision-making, the magnitude of an association and its clinical relevance, are not captured. In studies with large sample sizes, and a statistical analysis plan that is parsimonious and predetermined, most observed differences will not have occurred by chance (or bias), and the  $p$ -values will be concomitantly small. However, if a risk factor produces only a trivial change in the outcome of interest, then it is not important, regardless of how small the  $p$ -value is. Conversely, where a small study produces nonsignificant  $p$ -value, then this is not a convincing evidence that there is no relationship. Often, it simply reflects that the study was underpowered.

There are some specific types of cross-sectional data that require specific considerations. Repeated cross-sectional analyses over time can be used to effectively examine trends in prevalence for a given population. Survey data are commonly used for this purpose and represent a unique type of cross-sectional data. Survey data are specifically constructed so that individuals are sampled from a population based on attributes such as their location of residence or age. By carefully planning the selection of individuals, it is possible to determine the probability that a particular person is sampled. With this information, a weighting can be attached to individual observations, and by applying these weights to subsequent analyses, we can produce results that more accurately extrapolate to population level. These methods can be of use in reducing the number of individuals required to produce an accurate estimate and allow for oversampling in particular groups of interest where we might desire more accurate estimates. When reading an analysis of survey data, it is important to check that the appropriate adjustments were made to account for the study design, for example, using replicate weights (Levy and Lemeshow 2008). It is also important to check that this weighting has been calculated correctly. This can be accomplished by checking the calculation of known population characteristics against other data.

For almost all study types, including cross sectional, there are specific reporting guidelines designed to ensure that all the necessary information for critical appraisal are provided. Cross-sectional studies are covered by the Strengthening Reporting of Observational Studies in Epidemiology (STROBE) guidelines (von Elm et al. 2008). Similar guidelines exist for most study types and can be found online at <http://www.equator-network.org> (Simera et al. 2010). Reporting guidelines aim to ensure that the relevant pieces of information to assess bias are provided, but they are not designed to assess study quality. Where

study quality needs to be formally assessed (e.g., for a systematic review or clinical practice guideline), there are separate risks of bias tools available, such as the Newcastle-Ottawa Scale for nonrandomized studies (Wells et al. 2012).

**Notable Studies**

The Bogalusa Heart Study is an example of a study that uses cross-sectional data (among other types of data) to answer specific questions (Table 3). One resultant 1976 paper described the prevalence of hypertension in a single US community. In this paper, it was found, contrary

**Table 3** Key clinical studies of hypertension in children

Study	Study types	Year	Sample size <sup>a</sup>	Population	Important findings
Bogalusa	Cross sectional, cohort	1976 ongoing	3500	School-aged children (>5 years) in Bogalusa, Louisiana	Secondary causes of hypertension in childhood are now less common than essential The clustering and tracking of BP and other cardiovascular risk factors vary by race
Young Finns	Cohort	1985 ongoing	4000	Children aged 3, 6, 9, 12, 15, and 18 years at baseline were enrolled	Hypertension in childhood increases the odds of hypertension in adults by over 2× Arterial stiffness and CIMT is increased in adults with a history of hypertension in childhood
Muscatine	Cross sectional, cohort	1975 ongoing	11,000 (2500 followed)	Enrolled at 7–18 years of age	Left ventricular mass is related to BP in children Data pooled among Bogalusa, Young Finn, Muscatine, and CDAH studies confirm that childhood BP predicts CIMT in adult life
Raine	Cohort	1993 ongoing	2800	Birth cohort	Pregnancy-induced hypertension is a strong predictor of hypertension in young adult offspring BMI trajectory, as well as absolute BMI, through childhood influences adult BP
NHANES	Cross sectional, cohort	1971 ongoing	1500–4000 <sup>b</sup>	Population-based survey. BP in children >8 years	The prevalence of hypertension is increasing, partially explained by an increase in obesity
ESCAPE	Randomized control trial	2009	385	3–18 years with GFR 15–60 ml/min/1.73m <sup>2</sup>	Targeting 24-h BP below the 50th centile reduces rate of progression of CKD as compared to a 24-h BP target of 50–95th centile

BP blood pressure, NHANES National Health and Nutrition Examination Survey, ESCAPE Effect of Strict Blood Pressure Control and Angiotensin Converting Enzyme Inhibition on the Progression of Chronic Renal Failure in Pediatric Patients, CIMT carotid intima medial thickness, GFR glomerular filtration rate, CDAH child determinants of adult health

<sup>a</sup>For cohort studies, this changes with time and outcome, approximate starting sample size is listed

<sup>b</sup>Missing data rate for BP ~50%

to previous belief, that the majority of hypertension was now primary in origin (Voors et al. 1976). The authors accurately quantified the problem at hand, allowing them to then make a cogent argument for future prospective work in the field. Information was also provided regarding potential risk factors for hypertension such as race and body mass index. The Bogalusa study has continued to follow participants and is now a source of prospective cohort data. In 1995 the group began publishing data on BP tracking over more than 15 years (Bao et al. 1995). As more observations have been accumulated on individuals, longitudinal methods of data analysis can be used to differentiate the relative impact of different risk factors at a more granular level. Recent Bogalusa analyses have confirmed that obesity beginning in childhood is a key predictor of the future development of metabolic syndrome and that cardiovascular risk factors tend to cluster more closely among blacks than whites (Chen et al. 2007).

An important example of survey data is the National Health and Nutrition Examination Survey (NHANES) in the USA. The origins of NHANES can be traced back to the National Health Survey Act of 1956, when the National Center for Health Statistics was authorized by Congress to investigate the prevalence, distribution, and associations of malnutrition in the USA (Miller 1973). Subsequently, several surveys were merged to form NHANES in 1971–1974, and then in 1999, the structure of NHANES was changed such that it became a yearly, ongoing survey of around 5000 participants (Johnson et al. 2013). NHANES is an important source of public health data in the USA and internationally. The methodology for taking BP has remained constant since 1988, and NHANES is sufficiently large to produce precise prevalence estimates. Large surveys are of interest to those involved in public health, where it is advantageous to identify emerging patterns of disease early on, before they reach epidemic proportions. As applied to pediatric hypertension, the beginnings of an epidemic and its correlation with childhood obesity have been demonstrated by multiple authors using NHANES data (Din-Dzietham et al. 2007; Rosner et al. 2013).

## Diagnostic Test Accuracy Studies

These represent a specific subtype of cross-sectional study. Normally they consider the application of a new or index test against a reference standard (also known as a gold standard) that defines the presence or absence of disease. The ultimate aim is to discover an ideal test that is not only accurate and widely available but also acceptable to the population due to minimal invasiveness and discomfort and of acceptable cost.

There are a number of different ways to express test accuracy. Standard measures include sensitivity, specificity, positive predictive value and negative predictive value. Sensitivity refers to the proportion of people with disease that are correctly classified by a test. Specificity refers to the proportion of people without the disease who are correctly classified. To consider the practical implications of these test characteristics, it is necessary to know the baseline prevalence of the condition being tested for and the downstream consequences of false positives and false negatives. For a rare condition (e.g., pheochromocytoma), where the prevalence is low, the specificity of a test becomes relatively more important than for a common condition. In such a scenario, a test may be highly sensitive, but if it lacks specificity, a positive result is most likely to be due to someone without disease returning a false-positive result (high false-positive rate), leading to additional unnecessary tests. The impact of baseline prevalence on test utility is expressed in the positive and negative predictive values. These measures reflect the proportion of people with a given test result that have been correctly classified. Put another way, the positive predictive value is the proportion of people who test positive that actually have the disease in question.

### How to Read

When assessing the quality of a diagnostic study, start with the question being asked. A modified PICO-type format can be used here: population, previous tests, index test (that being studied), comparator (where multiple or replacement tests are being considered), and outcome (reference test result) (PPICO). It is important to be clear where

in the diagnostic pathway the proposed test fits. The performance of a test will vary according to whether it is being used as a screening, replacement, or add-on test (Bossuyt et al. 2006).

Then consider the selection of patients into the study. A case-control design, while necessary for some rare diseases, is prone to spectrum bias and is best avoided (Whiting et al. 2011). Spectrum bias exists where a test compares patients who clearly have disease against those who clearly do not. By excluding patients with less severe disease or other potential diagnoses, the test performance is overestimated because most tests will perform less well in these more difficult to diagnose or intermediate-spectrum patients. Spectrum bias can be avoided by enrolling a sample of consecutive patients in whom the test would be applied in normal clinical practice. If a specific subgroup of patients is deliberately being considered in the study, then the applicability of the results to other patient groups may be limited (Leeftang et al. 2013).

Verification bias is another common finding. There are two forms, partial and differential verification bias. Partial verification bias is where only some patients receive the reference standard. Most commonly this occurs in patients with a negative index test, leading to the exclusion of some false-negative patients, because the reference test is expensive and/or invasive, and so it is avoided. This acts to increase the observed sensitivity of the test (Whiting et al. 2013). Sometimes limited application of the reference test is justified because it is invasive or carries risks that make it unethical to apply to cases with a negative index test. In such instances, it is preferable to introduce the potential for differential verification bias, which is where a different reference standard is used for some participants (Reitsma et al. 2009). For example, patients with a negative screen for cancer may be followed for a period of time to see if they develop clinical disease instead of undergoing biopsy (a two-step reference standard).

Some other important biases to consider in studies of diagnostic test accuracy are incorporation, test review, and diagnostic review bias. Incorporation bias is where the index test is included in the reference test (often a composite measure) and acts to increase test accuracy

because a test is effectively being compared against itself. Test review bias occurs where those determining the index test result are aware of the outcome of the reference test. Diagnostic review bias is the reverse, where those assessing the reference test are aware of the index test results. Both of these biases could increase or decrease test accuracy, dependent on the assessor's prior beliefs about the tests in question.

Intermediate or ambiguous test results should be included in the determination of test accuracy, because this mirrors real life. In everyday practice, there will be results that are not interpretable; these test results do not aid in our diagnosis, and so their frequency is of relevance to the utility of a test. Normally, a best-worst type analysis is performed, where ambiguous results are assumed to be correct and subsequently incorrect, producing a range of possible test accuracy under these assumptions. Leaving patients out who have these ambiguous results typically leads to an overestimation of test performance.

### Notable Studies

Diagnostic test accuracy studies need not to consume a large amount of resources or be overly complex. For example, part of the 1976 Bogalusa study considered the accuracy of an automated oscillometric BP device compared with a mercury sphygmomanometer. In their recent recommendations and review, the US Preventative Services Task Force (USPSTF) identified a gap in the evidence regarding the diagnostic test accuracy of office BP in well children (Moyer and USPSTF 2014). They were able to identify only two studies that examined the test accuracy of office BP in well children (Fixler and Laird 1983; Stergiou et al. 2008). These both demonstrate a modest accuracy for office BP as a screening test. Based on these data (sensitivity of 65% and specificity of 75%) and a 5% prevalence of hypertension, the USPSTF points out that of 26 children who test positive, only three would have hypertension (Thompson 2014). Another recent systematic review came to similar conclusions (Chiolero et al. 2013). The importance of this low positive predictive value depends upon how one views the risks and benefits of a positive test result.

The USPSTF was of the opinion that the cost arising from a large number of false-positive tests (repeat reviews, anxiety) might outweigh the benefit of early detection in the relatively small number of true positives. This contrasts with the recent European Society of Hypertension guidelines that considered the consequences of a false-positive low, compared with the benefits of early detection through screening, and so recommend measuring office BP every second year from the age of 3 (Lurbe et al. 2016).

A problem regarding the current evidence base for the accuracy of BP screening in children is that the majority of studies to date have enrolled selected populations of children. These are mostly children who have either been previously identified as hypertensive or who have preexisting diseases that place them at increased risk. This limits the generalizability of findings because the accuracy of tests may vary substantially depending upon their setting (Leefflang et al. 2013).

## Cohort Studies

Cohort studies follow the same sample of the population over time. They can be retrospective, looking back at events that have already occurred, or they can be prospective, following a population forward in time. Cohort studies provide further information on, but not definitive evidence of, causality by chronologically linking outcomes and explanatory variables of interest. In some instances, it is highly impractical or impossible to conduct a randomized control trial (RCT), leaving cohort studies as the highest, single study level of evidence available for questions of causal inference (as compared with a systematic review of all possible studies).

## Strengths and Weaknesses

A fundamental strength of cohort studies is the ability to chronologically link risk factors and events. This increases our ability to make inferences about causation but falls short of proving them, because of unmeasured influence of confounding in our final estimates of effect, termed residual confounding.

In a retrospective study, we are often unable to gather information on all of the important potential confounders of interest. It might be that we are using a data from a study that investigated an entirely unrelated hypothesis or registry data that is limited in the demands it can impose on data entry. In this instance, there will be known confounders for which we are unable to adjust our estimates. In contrast, a prospective cohort study can collect information on all relevant covariates of interest. This is a substantial advantage and means that we have the opportunity to more fully adjust for known confounding variables, although there remains an element of residual confounding due to inaccuracies or limitations in the data. These limitations should be acknowledged when interpreting the results and consideration given to the likely direction and strength of the resultant bias.

In some ways, a more sinister source of bias that can never be eliminated from cohort studies results from the presence of unknown confounders. These are variables that are unequally stratified by the explanatory variable of interest but are related in ways we are not aware to the outcome of interest. This unavoidable element of residual confounding presents one of the main reasons to perform RCTs.

## How to Read

Apart from residual confounding, other potential biases may be evident (Table 2). A common problem in studies that follow participants over a long period of time is loss to follow-up and consequentially, missing data.

When examining the impact loss to follow-up might have had on study results, we need to consider whether the loss has occurred in a differential manner between groups (stratified by the covariate of interest). This will determine the direction and degree of the resulting bias. If participants are lost in a manner that is completely at random, then their missing data will not influence results, aside from a reduction in precision. However, it is often the case that those who are at highest risk or belong to a particular subgroup are more likely to be lost to follow-up; for example, patients with aggressive disease or who

experience adverse effects from a treatment are more likely to be lost. This introduces a differential bias, termed attrition bias, to our results. Attrition bias has the potential to lead to either type one (to incorrectly refute the null hypothesis and thus incorrectly conclude a relationship exists where one does not) or type two error (to incorrectly accept the null hypothesis) depending on the characteristics of the participants lost.

Given the potential impact of attrition bias, the loss of participants to follow-up is best avoided if possible. This can be mitigated through regular study visits, engaging participants in the project (through information sessions and publications to highlight the importance of their contribution) and making data collection as convenient as possible for participants (e.g., by conducting study visits at distant sites). Data linkage strategies that use routinely collected health and administrative data are becoming more commonplace and can minimize the amount of missing data when participants are lost to conventional, in-person follow-up.

Some missing data is inevitable, and there are a number of statistical techniques available to handle missing observations. Some of these are to be avoided as they are known to introduce bias of their own into the results, such as last observation carried forward (Saha and Jones 2009), but there is an increasing acceptance that some newer techniques such as multiple imputation can reduce bias and improve the reliability of results (Little et al. 2012). These should at a minimum be applied as sensitivity analyses when considering the impact missing data might have had on the study results. The method of final analysis is also important because some statistical methods are more robust to missing data than others (e.g., likelihood-based mixed models and generalized estimating equations) (Fitzmaurice et al. 2011).

When considering longitudinal cohort data, it makes sense to apply longitudinal methods of data analysis. By using all the available data, longitudinal methods normally have increased statistical power to detect an effect and can then describe this effect in more detail. In the setting of hypertension in children, longitudinal analyses aim to predict the course of BP over time rather than at a single timepoint in adult life. There are many

techniques for modelling longitudinal data such as trajectory-based modelling. Random effects models and generalized estimating equations have been accepted within the statistical literature for decades. However, despite their potential utility in analyzing longitudinal data, the uptake of methods of correlated data analysis among clinical researchers has been slow, outside of obvious applications such as cluster trials (Wood et al. 2004). This might be due to a greater level of statistical training being required to undertake such analyses or perhaps that reviewers and readers without training in these methods are skeptical of their application and results. This is unfortunate, because longitudinal methods take advantage of all the data collected, can describe the functional form of the outcome over time in relation to covariates of interest, and allow for a partial contribution to the results from participants who are lost to follow-up.

### Notable Studies

Data describing the natural history of hypertension in children are beginning to emerge from several different study cohort studies, many of which are ongoing (Sun et al. 2007; Rademacher et al. 2009; Juhola et al. 2011; Huang et al. 2015; Kagura et al. 2015; Theodore et al. 2015). In particular, it has been shown that hypertension in childhood tracks closely into adult life. An excellent example of a cohort study is the Young Finns Study, begun in 1980 and which continues to produce data. Like the Bogalusa study, the Young Finns Study had its genesis in cross-sectional data that identified a high incidence of cardiovascular disease in the population (Pyörälä et al. 1985). Around this time, the WHO recommended that long-term cohort studies into the origins of cardiovascular disease were needed, noting that the atherosclerotic process begins early in life (Raitakari et al. 2008). By following participants over a long period, the group has determined the ability of hypertension in childhood to predict hypertension in adult life (Juhola et al. 2011). They have demonstrated that the odds of having hypertension in adulthood are increased 2.3 times (95% CI, 1.1–5.2) for 6–9-year-old hypertensive children and 2.4 times (95% CI,

1.6–3.5) for 12–18-year-old hypertensive children. Similar results have been demonstrated in other longitudinal cohorts, quantifying the risk associated with childhood hypertension for later in life (Shear et al. 1986; Lauer and Clarke 1989; Sun et al. 2007; Juhola et al. 2013).

A good example of longitudinal data analysis is the application of trajectory-based modelling to data from the Dunedin Multidisciplinary Health and Development Study (Theodore et al. 2015). In this publication, children with similar BP trajectories from age 7 to 38 years are identified using a group-based trajectory model. The authors then investigate early life risk factors that identify which children are likely to follow a hypertensive trajectory. They are also able to examine variables that modify BP for children that are tracking within a particular group. Another example of trajectory modelling comes from the Raine Study group who considered the effect of different obesity profiles over childhood on adult BP (Huang et al. 2015).

## Randomized Controlled Trials

The only way to truly determine if a relationship seen in observational data is causal in nature is to conduct RCTs. The randomization process ensures that the patients in each group of a trial are equal in all aspects aside from the desired intervention (if large enough). Therefore, any observed difference in the outcome can only be due to the intervention. RCTs provide the highest, single trial level of evidence with which to inform clinical decision-making.

### Strengths and Weaknesses

The first RCT of the modern era to be conducted was performed in 1948 to assess the effects of streptomycin in pulmonary tuberculosis (Streptomycin in Tuberculosis Trials Committee 1948). This trial was undertaken by the Medical Research Council in the United Kingdom, in part because of a limited supply of this new drug and because previous case reports and poorly controlled trials had led to a proliferation of treatments without benefit, including gold. The

methodology of this trial was robust by any standards and demonstrates the seemingly perfect simplicity with which an RCT can answer a specific clinical question.

The most important limitations of RCTs, within present-day research structures, are the enormous financial cost and logistical difficulty involved. This problem is exacerbated in pediatrics, where sample size normally dictates trials be multicenter and often international in scope.

Fortunately, new trial designs continue to be developed that improve efficiency. For example, the platform trial design that is adaptive in nature and so continually evolves to evaluate new therapies, or stepped wedge, clusters trials that attempt to maximize the statistical efficiency of a traditional parallel-arm, cluster trial (Woertman et al. 2013). An important trend in modern trial design is an increasing use of pragmatic trials. These can be broadly considered as trials where the interventions being delivered are consistent with routine clinical practice and in which the additional demands on clinicians and patients imposed by involvement in the study are minimal. Pragmatic trials are expanding in popularity, in line with the evolution of electronic health records that should allow for easy, inexpensive patient follow-up. Proponents argue that whenever we lack sufficient evidence to make an informed treatment decision (including comparative drug trials), then it is unethical not to have patients enrolled in a trial. Thus, it is problematic that one of the current limitations to more pragmatic trials being performed is a seemingly heavy-handed approach taken by institutional review boards; when in routine care, no ethics approval is required (Pletcher et al. 2014). This occurs even for trials comparing therapies that are already widely applied in clinical practice and using data that would already exist via electronic health records (Staa et al. 2012).

A weakness in the application of trials overall is that children are often excluded. To better understand why this is the case, we need to consider more broadly how children are accommodated within present structures surrounding the organization and conduct a clinical research. The cost of clinical trials continues to balloon, and investigators are discouraged by an increasing



burden of paperwork (Caldwell et al. 2004; Eisenstein et al. 2008). This discourages both sponsors and clinicians from conducting and also skews the spectrum of trials to those that are more commercially desirable. To reduce costs and increase the likelihood of obtaining a positive result, clinical trials aim to recruit groups of patients with high event rates in whom data is easy to collect. As a result, children are often excluded from trials (Van Spall et al. 2007). This disadvantages the pediatric population through potential delays in access to novel therapies and a lack of directly translatable evidence (Emanuel 2000; Caldwell et al. 2004). Of note, the paucity of pediatric evidence is made more important by systems of post-market monitoring that are limited in their ability to detect risk signals, particularly for drugs that are being used outside of their licensed indications, which is commonly the case in children (Impicciatore et al. 2001; Fontanarosa et al. 2004).

### How to Read

Some design and conduct features are unique to trials. To begin with, the process of randomization itself should not introduce any differences between groups. For example, a “randomization” sequence based on days of the week will lead to group allocations that reflect the disease severity of patients presenting on different days of the week (e.g., on a Monday after a weekend when healthcare is deferred). To avoid such problems, the randomization sequence used to allocate patients should be generated completely at random. Tables of random numbers are appropriate but have largely been replaced by random number generators available within common computing programs.

It is possible, and often the case, that some nonrandom elements are included in the sequence generation process. The aim of these methods, such as permuted blocks and more complex dynamic minimization strategies, is to avoid chance imbalances in important known confounders. Chance imbalances have the potential to undermine the results of smaller trials. Although unlikely in large trials, imbalances occurring early on in the enrollment process

could influence interim safety analyses, potentially resulting in premature trial termination.

After the generation of a random sequence of treatment allocation, it is then necessary to conceal this sequence from researchers. This part of the trial process is known as allocation concealment. There is a large body of qualitative and quantitative literature regarding the importance of allocation concealment. Healthcare professionals will go to extreme lengths in attempts to derive what they perceive as the best care for their individual patient. Hence, reports of clinical staff holding envelopes up to intense light, noting subtle difference in study medicine labels or even opening non-numbered allocation envelopes, should be of no surprise to researchers (Schulz 1995). The manifestation of this is that allocation concealment can be shown to be more important than other commonly assessed domains of bias such as blinding and sequence generation, particularly in smaller trials (Schulz et al. 1995; Kjaergard et al. 2001).

The process of blinding in trials is conventionally regarded as a different issue to that of allocation concealment and again is unique to the trial design. The concern here is that if those involved in the care of patients or analysis of data discover a participant’s treatment allocation, then they may perform differently, either in a clinical context (performance bias) or in the process of measuring data (a form of measurement bias). For this reason, participants’ treatment allocation is often hidden from the staff involved in a study. The staff are then said to be blinded (or masked) to the treatment allocation. One common example of blinding would be the use of a placebo in the control arm of a trial to hide the treatment allocation from participants and healthcare providers. When describing blinding in a clinical trial, the term double blind is rarely helpful, because there are more than two groups of people who need to be blinded. They include patients, healthcare providers, data collectors, and data analysts. The unmasking of a participant’s treatment allocation at any point in the chain of clinical care, data collection, or data analysis has the potential to compromise results. Objective rather than subjective end points have less potential to be affected

by a lack of blinding. Thus, they are preferable where it is not possible to initiate or maintain blinding, such as in many surgical trials.

When reading a publication of trial results, close attention should be paid to the choice of outcome measure. Outcomes should be directly relevant to patients, and of clinical importance. Of note, there is a push to establish a core set of outcomes that are patient relevant and reported consistently across trials in nephrology. The Standardized Outcomes in Nephrology Group (SONG) has begun this process, for people on hemodialysis, transplantation trials, and more recently for children with chronic kidney disease (Tong et al. 2016).

The choice of an appropriate outcome can be further complicated where important end points may not be feasible, for example, when studying the impact of treating hypertension in childhood on distant cardiovascular events. In this case, the only realistic trial is one where surrogate measures for the outcome of interest are used (e.g., use of proteinuria reduction as a surrogate for decreased progression of glomerular disease). Studies relying on surrogate outcomes should be approached with caution, because we also need to consider the uncertainty involved in translating results to clinically relevant patient outcomes. This uncertainty is reflected in the fact that it is not uncommon for drugs approved based on surrogate outcomes to fail to demonstrate clinically meaningful benefit once in routine/widespread use (Kim and Prasad 2015; Svensson 2016). In general, surrogate outcomes are positive and favor the intervention, but examples where clinically relevant end points concord with the surrogate are remarkably infrequent (Ciani et al. 2013). In nephrology, the use of surrogate outcomes is common. This is particularly the case for trials of antihypertensive agents, despite there being little evidence linking common surrogates such as left ventricular mass and patient relevant outcomes (Badve et al. 2016).

Composite outcomes are also used to increase power and reduce cost compared to a single outcome measure. For example, the progression of renal disease might be represented by a combination of doubling of estimated glomerular filtration rate (GFR) and proteinuria or the initiation of

renal replacement therapy (RRT). As for surrogate outcomes, it can be difficult to interpret the clinical importance of composite outcomes. It is often observed that the magnitude and direction of the composite outcome differ from those of its individual end points (Schulz and Grimes 2005). A systematic review of composite outcomes from trials published in 2008 found that end points of differing clinical significance were combined in 70% of trials (Cordoba et al. 2010).

The choice of outcome measure has important implications for study design. In addition to looking for an outcome that is valid and patient relevant, researchers also try to maximize the statistical efficiency of their trial. In this regard, there are advantages to ambulatory blood pressure monitoring (ABPM) as the method of measurement where BP is the outcome of interest. While ABPM is a more demanding end point to collect, the elimination of masked hypertension will reduce the measurement error and thus the sample size required to detect a treatment effect.

The intention-to-treat (ITT) principle is another important concept to consider when assessing the validity of a trial. There is a temptation at the end of a trial to analyze patients according to the intervention that they received (per-protocol or as-treated analysis), rather than that to which they were assigned (intention to treat analysis). Outside of a non-inferiority trial, this should be avoided because it potentially reintroduces selection bias and a non-differential distribution of known and unknown confounders between groups. This is in part because patients who drop-in or dropout of groups in a trial may have specific reasons for doing so. Where treatment allocation and/or blinding have been compromised, then physician or patient preferences can distort group allocation. Similarly, adverse effects or a lack of perceived benefit from the assigned treatment regimen may drive drop-in and dropout. These are some of the reasons that per-protocol analyses may be based on groups that are no longer randomly distributed and have been shown on average to lead to increased estimates of effect (Porta et al. 2007).

In addition, the external validity and thus clinical relevance of per-protocol analyses are limited

because the analysis is no longer relevant to physicians and patients at the point of decision-making in clinical practice. One does not know how a specific patient will respond to a particular treatment ahead of time or even necessarily who will be adherent with a particular prescription. This is not to say that there is no situation under which a randomized participant can be legitimately excluded from the final analysis of a trial. For example, patients who are mistakenly randomized into a clinical trial despite not meeting eligibility criteria may be excluded without introducing bias, provided the decision is made entirely independently of the patients' clinical course following randomization (Fergusson et al. 2002).

The interpretation of results where the primary outcome does not achieve statistical significance requires special consideration. Reasons for this include a lack of statistical power, bias toward a type two error, and that the intervention in question actually has no effect. Phase three trials should be based on a sample size that provides sufficient power to detect the smallest clinically relevant difference between groups. Sample size calculations should be performed to assess the power of a trial and should be reported. This refers to a chance that a difference between groups will be detected where one truly exists (one minus the type two error rate). It is often set at 80%, which means that there is a one in five chances that the trial will return a false-negative result. So chance may produce a negative study result, just as bias can increase the type one error rate of a trial (away from the null hypothesis); it can also act to increase the type two error rate (toward the null hypothesis). For example, if there are difficulties in blinding patients, some people will dropout of the control group and drop-in to the treatment group. If the treatment is effective, then this movement of patients will reduce the ability of the trial to detect an effect. Another explanation for a negative study result is that there truly is no difference between groups. The majority of treatments that appear promising in laboratory and early clinical studies are not ultimately found not to be effective in clinical practice when formally tested. Researchers from pharmaceutical companies, who have a commercial interest in the

reproducibility of preclinical studies, have found that only 10–25% of studies can be reproduced in their own laboratories (Prinz et al. 2011; Begley and Ellis 2012). This is thought to be due to differences in translating basic science from laboratory experiments performed in different species to humans but probably also reflects problems with selective reporting (only reporting the significant results in a set of experiments) and publication bias (to be discussed later). Given this, from a Bayesian perspective, if sufficiently powered, when well-designed trials fail to detect a difference in treatment groups, then the intervention is unlikely to be effective. In this case, it is unethical to waste scarce research resources on further trials unless new evidence comes to light (Chalmers et al. 2014).

### Notable Studies

There is a paucity of trial-based level evidence relating to hypertension in children. However, it is possible to perform trials in this population, as demonstrated by the Effect of Strict Blood Pressure Control and Angiotensin Converting Enzyme Inhibition on the Progression of Chronic Renal Failure in Pediatric Patients (ESCAPE) group (Wühl et al. 2009). In this trial, 385 children with a glomerular filtration rate between 15 and 60 ml/min/1.73m<sup>2</sup> were randomized to a target of 24-h mean arterial pressure of less than 50th centile versus 50–95th centile, after the application of maximal dose of ramipril. The results demonstrated that 29.9% of children in the intensive BP control group versus 41.7% in the standard target group had a 50% decline in estimated GFR or started RRT over 5 years of follow-up (hazard ratio 0.65, 95% confidence interval 0.44–0.94). In total 33 European centers participated. ESCAPE is an example of what is possible with multicenter collaboration.

### Systematic Reviews and Meta-analysis

The term systematic review refers to a specific process, whereby a comprehensive and clearly defined strategy is used to identify and then synthesize all the relevant literature required to

answer one or more discrete questions. As part of a systematic review, it may be possible to perform a meta-analysis. There are different statistical methods of meta-analysis, but they all serve to combine the results of individual trials to produce a single summary estimate with surrounding confidence intervals. A well-performed systematic review provides the highest possible level of evidence on which to base decisions.

### Strengths and Weaknesses

The process of systematic review and meta-analysis stands in contrast to that of narrative review, in which there are no clearly defined methods for study inclusion and no objective outcomes produced. Thus, it should come as no surprise that narrative reviews have been shown to produce conclusions that are more prone to bias than systematic reviews (Barnes and Bero 1998). Narrative reviews have also been shown to lag behind systematic reviews in identifying appropriate evidence-based interventions (Antman et al. 1992). While RCT data are more clearly amenable to systematic review, the methodology can be successfully applied to almost any study design including observational studies.

The importance of systematically reviewing and summarizing all the available evidence when attempting to answer clinical questions cannot be overemphasized. The use of systematic reviews has been championed in part by the Cochrane Collaboration. This is an international not-for-profit organization that provides unbiased systematic reviews for consumers and healthcare providers. Their reviews have been shown to be on average of higher quality and less prone to bias than other systematic reviews, particularly when compared to those where there is conflict of interest due to industry funding (Jadad et al. 2000; Jørgensen et al. 2006). The Cochrane Collaboration logo (Fig. 1) contains within it a forest plot taken from a meta-analysis demonstrating the beneficial effect of antenatal steroids on neonatal mortality in premature babies. This plot was chosen as an example where a systematic review was pivotal in the implementation of a life-saving practice, after years of smaller studies failed to translate it into clinical practice, possibly because



Fig. 1 The Cochrane Collaboration logo

of a dilution of the literature with underpowered studies that failed to show benefit (Crowley 2000). There are many examples of similar situations in the literature. One other striking example is the use of thrombolysis for acute myocardial infarction. Cumulative meta-analysis demonstrated a benefit of thrombolysis in 1971 at  $P < 0.05$  and clearly demonstrated benefit in 1977 at  $P < 0.001$  (Antman et al. 1992). However, in reality meta-analysis was not performed until the early 1990s, and so there was a delay of over 20 years in the implementation of this effective therapy. The importance of systematic reviews will only increase in the future as the quantity of medical literature continues to expand.

The inclusion of a systematic review in the publication of a trial facilitates and encourages research to be placed in context (Clarke et al. 2010). This needs not be an exhaustive Cochrane style review in all cases. As the Lancet has demonstrated, authors can be obliged to provide evidence of a systematic approach to identifying, appraising, and consolidating previous trial results when reporting their own.

Despite the potential benefits of systematic reviews and meta-analysis, there remains a reluctance in some quarters of academia to accept these techniques (Chalmers 2005). This may be because, as with any scientific method, systematic reviews are susceptible to flaws in methodology and cannot always provide all the answers we are looking for. There is wide variation in the quality of published systematic reviews, and increasing numbers of poorly conducted systematic reviews

have the potential to “pollute” the literature, as is the case with primary studies (Jadad et al. 2000; Moher et al. 2007).

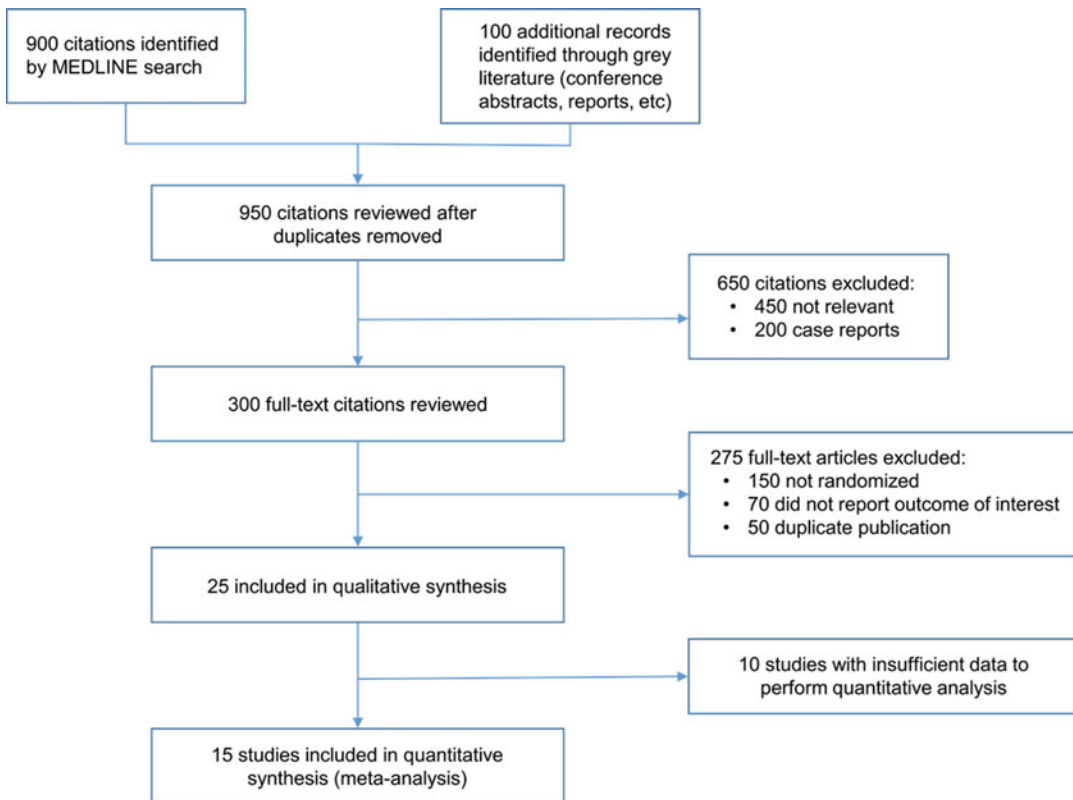
### How to Read

Important components of a systematic review include the question being asked (is it clear and specific enough to answer the clinical question), the inclusion and exclusion criteria, the search strategy used (should be clear, reproducible, and broad enough to capture all relevant studies), and the study flow diagram (the results should be consistent with the question and other methods; see Fig. 2 for an example) and were key steps such as the selection of studies performed by at least two independent reviewers and what was their level of agreement (a high level of agreement suggests a valid review process), have the authors considered the impact of bias and quality among included studies, and have clinical

and statistical heterogeneity been adequately explored.

Where a review is well conducted, our confidence in the final results will depend upon the quality of the included trials, consistency of results, and precision surrounding the summary estimate of effect. Authors should make it easy for readers to identify information pertaining to trial quality by clearly displaying their assessments of included trials. A standardized tool such as the Cochrane risk of bias tool for trials or the Newcastle-Ottawa Scale for nonrandomized studies should be used. In addition to grading the quality of included trials, it is necessary to consider any impact that trial quality might have had on the outcomes of the review. Sometimes, where there are ample data, a review might include only high-quality studies.

An important sign of a well-conducted systematic review is a thorough examination of



**Fig. 2** Example study flow diagram

heterogeneity (the amount of variation in trial methods and results). The presence of heterogeneity can allude to differences in important trial characteristics that prohibit the pooling of results. Heterogeneity can also be useful in the process of systematic review, for example, by highlighting subgroup effects. Where a meta-analysis has been performed, the heterogeneity present between trials can be quantified. Different tests exist, but one useful measure is the  $I^2$  value. This reflects the percentage of the variation in results explained by between-trial differences alone (Higgins et al. 2003). A value of greater than 30% may represent moderate heterogeneity, whereas 75–100% represents considerable heterogeneity. These cutoffs are not fixed and do not mean that the trials being considered should or should not be pooled. Rather, the  $I^2$  result alerts us to the presence of between-trial differences that may or may not be important. In this way the  $I^2$  test can be applied to the examination of subgroup differences. For example, if the effect of antihypertensive agents on cardiovascular mortality was being considered, and there was a high level of heterogeneity between groups of trials considering different drugs, then it would be reasonable to suspect that different drugs have a different association with cardiovascular events. This technique avoids the inflated type one error rate associated with performing multiple hypothesis tests.

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement outlines the necessary components that need to be included in a review to allow readers to make an informed interpretation of the results (Moher et al. 2009). The PRISMA statement covers those aspects of a systematic review methodology discussed here and more. It also provides guidance on how to report results.

Systematic reviews are critical to the process of evidence-based medicine. However, they are not a panacea for poor quality or absent primary research. Because of this, systematic reviews are often unable to provide clear evidence. Despite this, if the process of systematic review is unable to identify sufficient literature to answer a specific question, then this information in itself is useful in

clarifying a need for further research. As such, systematic review is now demanded by some funding bodies prior to investing in new clinical trials (Chalmers et al. 2014; Bhurke et al. 2015).

It is also important to acknowledge that the evidence base available for systematic review can be influenced by publication bias. The results of trials may not be published for a variety of reasons at the level of sponsors, authors, and editors. One concerning example is where those with a commercial interest sponsor multiple trials but only publish those with a result favoring their product. The result is a systematic distortion of the evidence base producing a bias in subsequent meta-analysis. There have been efforts to minimize the number of studies that is not published via clinical trial registries and increasing conditions attached to government funding. However, the practice still appears to be occurring with relative impunity, as recent examples of withheld data on anti-influenza and antidepressant drugs demonstrate (Turner et al. 2008; Jefferson and Doshi 2014). More common at the level of researchers and journal editors is a tendency to prefer statistically significant findings and associations of greater magnitude. It is felt that smaller studies are at greater risk of nonpublication. A small-study effect can be observed in meta-analysis, whereby smaller trials have been shown to, on average, produce larger estimates of effect, which may also result from a greater susceptibility to errors in study design (Kjaergard et al. 2001; Dechartres et al. 2013). A funnel plot can be used to assess if the evidence on which a systematic review is based might be affected by publication bias or the small-study effect (Egger et al. 1997). However, interpretation is often hampered by a low power and a failure to account for heterogeneity in the included trials (Lau et al. 2006).

### **Notable Studies**

The recent USPTF recommendations on BP screening in well children were discussed earlier, in the context of studies of diagnostic test accuracy. As with any evidence-based process, these recommendations were informed by a systematic review (Thompson et al. 2013). The strengths and

weakness of this review have been debated elsewhere, and there has been criticism of the narrow inclusion criteria used, in a field where traditional RCT are not practical (Samuels et al. 2013; Urbina et al. 2014). However, despite having no specific expertise in the field of pediatric nephrology, the study group was able to identify almost all of the relevant literature to the questions posed (Thompson 2014). This suggests a sound search strategy and article selection process and highlights the utility of approaching the literature in a systematic way. At a minimum, this review has highlighted important gaps in the literature at present and should provide impetus for further research (Lo et al. 2014).

## Data Sharing

The pooling of study-level outcome data for meta-analysis is now an established part of the research landscape. However, if we believe in the combination of results and the sharing of data generated by clinical research, then it makes sense to go on and share data at the individual patient level. The most obvious benefit to sharing data at this level is that it greatly expands the detail with which we can consider and adjust for potential confounders. Data sharing also encompasses broader activities, such as opening datasets to secondary analyses.

There is now a clear consensus that data sharing is ethically desirable. As such, it is increasingly being mandated by regulatory authorities and soon the International Committee of Medical Journal Editors (Taichman et al. 2016). Proposed benefits of data sharing include the verification of initial statistical analyses, the creation of larger datasets that allow the earlier identification of true relationships through increased statistical power, the fostering of generation of novel hypotheses that can lead to well-directed future research, and the enhancement of transparency of clinical research (IOM 2015).

Take one proposed benefit that of the verification of research findings. After all, reproducibility is a key tenant of scientific investigation. There are repeated examples in the literature where

errors in initial data analysis, from simple coding errors to more complex statistical problems, have been uncovered by secondary investigators seeking to verify initial findings (Ebrahim et al. 2014; Chan et al. 2014; Davey et al. 2015; Le Noury et al. 2015; IOM 2015). It is difficult to truly know how much of the current literature is reproducible at the data analysis phase (let alone completely reproducible) without wider access to data. But it is quite possible that analytic problems are widespread, given the systematic biases and misconduct uncovered at other levels of the research process (Martinson et al. 2005; Fanelli 2009; Doshi 2015).

Data sharing is a particularly powerful approach when considering observational data and so will be important in the field of pediatric hypertension. Traditional meta-analysis does not typically account for differences between trials beyond the application of a between-study random effect. With access to individual patient data, we can model in detail the relationships between variables using similar techniques and those traditionally applied to single trials. To epidemiologists and clinical researchers seeking to accurately define the natural history of hypertension and the relative contributions of different risk factors, this level of detail is a key.

There is significant impetus behind data sharing, such that we are likely to see increased uptake regardless. Despite this, there are still some barriers that need to be addressed. Privacy is a major concern, and clearly data need to be de-identified to protect the privacy of participants. Aside from the ethical implications, any intrusion into privacy during these early stages of establishing data sharing could be catastrophic for the movement going forward.

Another potential issue is determining how to appropriately credit researchers involved in initial data generation. Ideally, secondary analyses will involve those who initially generated the data. They are best aware of its strengths and limitations, which are not always obvious from initial exploratory analyses and cannot always be easily conveyed through metadata (e.g., data dictionaries) (Merson et al. 2016). However, this will not always be possible. Thus, researchers are

concerned that their time and effort in generating the primary data will not be adequately recognized. It is likely that new mechanisms will need to be developed in response to properly acknowledge data generators where they are not actively engaged in the secondary analysis (Taichman et al. 2016).

If we are to engage in more widespread data sharing, then platforms and protocols will need to be developed that allow data to be shared and used in a meaningful way. Here, we can learn from our experience with clinical trial registries. While there was initial resistance to data registries, these have become useful enterprises in improving the overall quality of clinical research for the public good (Zarin et al. 2011). Nevertheless, the quality of the data that researchers are willing to submit remains a limitation, and certainly some trials are registered only to fulfil publishing requirements (Dickersin 2012). It will be important to determine what constitutes a minimum level of data and metadata to be shared in order to allow useful secondary analysis. As such, the application of common standards among researchers, data curators, epidemiologists, and others will be an important determining factor in producing useful data repositories (Bierer et al. 2016; Haug 2016).

In the short term, data sharing between research groups is already becoming more commonplace. In pediatric nephrology, the International Childhood Cardiovascular Cohort (i3C) Consortium has been established to facilitate the sharing of data among eight large prospective cohort studies that are examining the impact of childhood cardiovascular risk factors on adult events (Dwyer et al. 2013). Around 40,000 children were involved in these studies in their childhood during the 1970s and 1980s. By using data linkage, the incidence of cardiovascular events might be determined among the pooled cohort, now beginning to reach around 50 years of age. Realistically, this type of collaborative approach is the only way that the impact of childhood cardiovascular risk factors on the incidence of cardiovascular events in adulthood will be determined in the near future, and the group's efforts are to be applauded.

## Conclusion

The body of clinical research available to guide practice in pediatric hypertension is steadily growing. In the longer term, the cohort data necessary to accurately describe the natural history of BP from early childhood to adult life are beginning to come together. These will continue to advance our understanding of the progression to, and childhood risk factors for, adult hypertension and cardiovascular events.

Nevertheless, there are clearly some gaps in the literature as it stands. The controversy surrounding the recent USPSTF report suggests that some work still needs to be done to clarify the role of screening for hypertension in otherwise well children. Important pieces of information, such as the diagnostic test accuracy of office BP, could be rapidly produced by using existing data. No doubt, we will see a proliferation of such analyses specifically because of the USPSTF report and other recent systematic reviews.

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## Cross-References

- ▶ [Epidemiology of Cardiovascular Disease in Children](#)
- ▶ [Epidemiology of Primary Hypertension in Children](#)
- ▶ [Primary Hypertension in Children](#)
- ▶ [Sequelae of Hypertension in Children and Adolescents](#)
- ▶ [Value of Routine Screening for Hypertension in Childhood](#)

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# Changes in Drug Development Regulations and Their Impact on Clinical Trials

# 48

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## Abstract

Regulatory changes in the United States and Europe have stimulated major pediatric clinical trials of over 15 different antihypertensive agents over the last two decades. With increased pediatric hypertension trial experience, trial designs have been refined, and we now better understand factors associated with trial success or failure. Appropriate dose range, weight-based dosing, use of a liquid formulation, and use of appropriate blood pressure endpoints are all factors that have been associated with improved trial success. These lessons learned and important modifications in trial design templates are reflected in the United States Food and Drug Administration Written Request criteria. The Written Request provides valuable information that can be used to optimally design future clinical trials of

antihypertensive agents as well as other therapeutic agents for use in children.

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## Keywords

Pediatric hypertension • Clinical trials • Written Request • Pediatric exclusivity • Trial design

## Contents

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## Introduction and Review of Recent Regulatory Initiatives

Children have historically been underrepresented in drug trials with dosing, safety, and efficacy extrapolated from clinical trial data in adults. This practice is largely inappropriate, as children have unique differences in developmental drug pharmacokinetics and disease pathophysiology when compared with adults. Failure to account

for these differences risks safety events or sub-optimal efficacy.

Lack of clinical trial data in children has long been recognized as a major concern. In the 1970s, the American Academy of Pediatrics argued that failure to conduct drug trials in children was unethical (American Academy of Pediatrics 1977). However, regulatory initiatives enacted throughout the 1970s, 1980s, and early 1990s largely failed to address these concerns. To remedy this, in 1997, the US Congress passed the US Food and Drug Administration Modernization Act (FDAMA) including section 505A, known as the pediatric exclusivity provision (Food and Drug Administration Modernization Act 1997). The exclusivity provision granted an additional 6 months of patent protection to pharmaceutical companies in exchange for conducting pediatric trials in response to an FDA-issued Written Request. Subsequent regulatory initiatives including the 2002 Best Pharmaceuticals for Children Act (BPCA), the 2003 Pediatric Research Equity Act (PREA), the 2007 Food and Drug Administration Amendments Act (FDAAA), and the 2012 FDA Safety and Innovation Act (FDASIA) have further advanced pediatric drug development (Best Pharmaceuticals for Children Act 2002; Pediatric Research Equity Act 2003; Food and Drug Administration Amendments Act 2007; Food and Drug Administration Safety and Innovation Act 2012). Collectively, these initiatives established a system of incentives and mandates to encourage pediatric studies of on-patent drugs, off-patent drugs, and drugs not yet approved for marketing. For new drugs, the industry sponsor must submit a pediatric study plan (PSP) by the end of phase 2 testing. For drugs that are already being marketed and eligible for pediatric exclusivity, studies must be conducted as outlined in a Written Request. In this case, the Written Request is initiated directly by the FDA or in response to a proposed pediatric study request (PPSR) by the sponsor. Upon completion of these studies, the drug becomes eligible for 6 months of patent extension. Finally, for off-patent drugs, the FDA may create a Written Request to address a public health need, which is then sent to the appropriate industry sponsor. The sponsor may accept or

decline to perform the stipulated studies of the Written Request in return for pediatric exclusivity (U.S. Food and Drug Administration Pediatric Product Development 2016b).

Beyond creating a system for pediatric labeling, the pediatric labeling initiatives have mandated accountability for quality and tracking of pediatric studies. The results have been significant. In the United States alone >500 drug-labeling changes have been enacted for children including ten antihypertensive drugs with a new pediatric indication (Fig. 1) (Benjamin et al. 2006; Li et al. 2007; U.S. Food and Drug Administration New Pediatric Labeling Information Database 2016a). Highlighting the importance of these studies, approximately half of the products studied in the United States under FDAMA, BPCA, and PREA have been found to have substantive differences in dosing, safety, or efficacy in children when compared with adult populations (Rodriguez et al. 2008).

In Europe, a similar need for drug development studies in the pediatric population was recognized, and in 2006 the European Parliament passed the European Parliament Regulation No. 1901/2006 on medicinal products for paediatric use 2006 (Regulation (EC) No 1901/2006; European Medicines Agency Paediatric Investigation Plans 2016a). Based on this regulation, pharmaceutical companies must complete pediatric studies for any new drug following a pediatric investigation plan (PIP), which is similar to the Written Request in the United States. The PIP is reviewed by the European counterpart to the FDA, called the European Medicines Agency (EMA). Similar to the process in the United States, in return for completion of the PIP, a European sponsor receives 6 months of patent extension. The process of pediatric drug investigation for new drugs begins earlier in Europe, as manufacturers must submit a PIP after completion of phase 1 testing instead of after phase 2 in the United States. Finally, for off-patent drugs in Europe, companies can voluntarily develop a pediatric indication and formulation under a pediatric-use marketing authorization (PUMA). The development of a PUMA must follow a PIP, and in return, the sponsor stands to receive

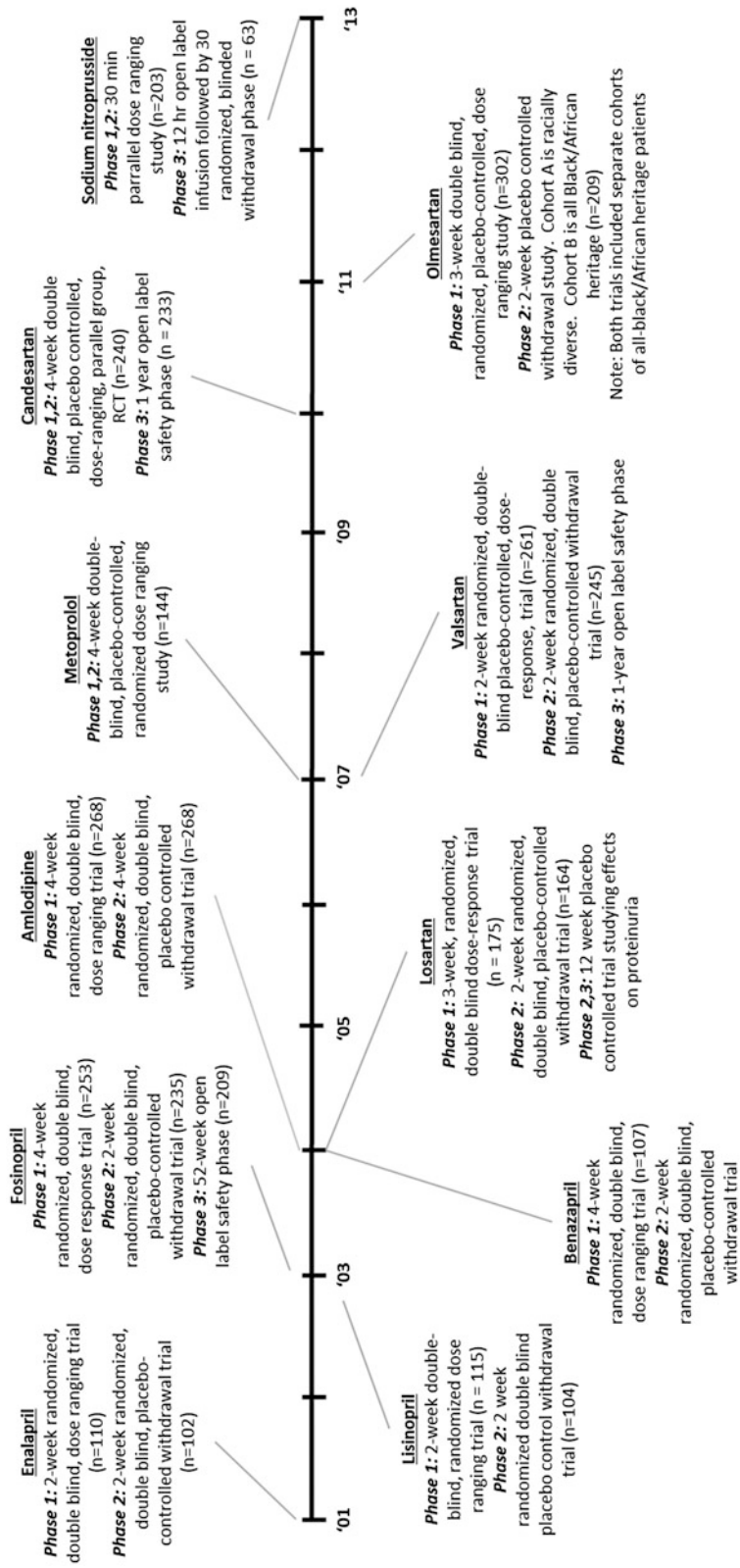
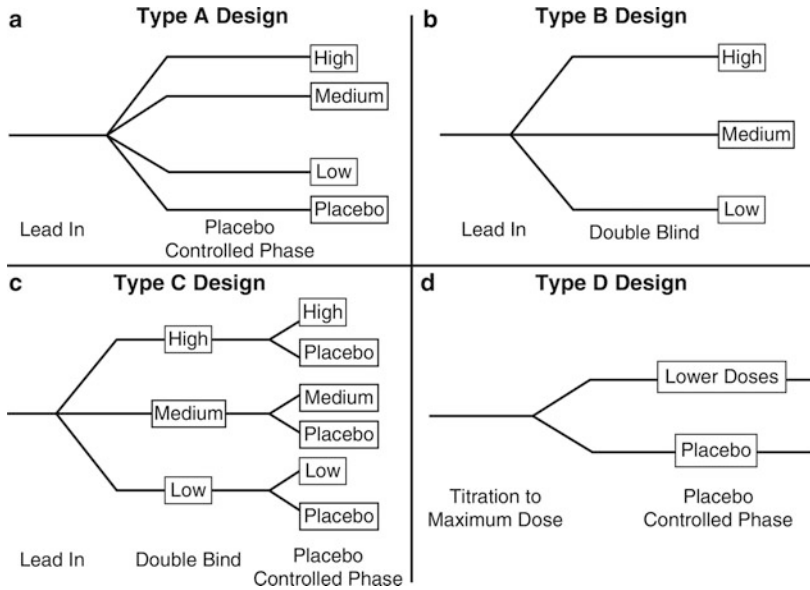


Fig. 1 Summary of drug trials that have resulted in a new labeled indication for treatment of hypertension in children and/or adolescents in the United States



**Fig. 2** Antihypertensive trial designs specified in the FDA Written Request criteria

10 years of marketing protection (European Medicines Agency Paediatric-use Marketing Authorisations 2016b).

Many similarities exist between the pediatric drug development programs of the FDA and EMA. Written Request (FDA) and PIPs (EMA) have been used to guide trials and are refined over time to reflect the current understanding of the best approaches to various pediatric clinical trials. This chapter will focus specifically on the impact of the FDA Written Request on pediatric hypertensive trial design and conduct, presenting an overview of the clinical trial design templates and requirements specified by the Written Request and reviewing factors associated with success or failure of prior clinical trials.

## Pediatric Antihypertensive Clinical Trial Design

The FDA strategy typically calls for (1) a dose-ranging trial in hypertensive pediatric patients; (2) pharmacokinetic trials in four pediatric age groups: infants and toddlers, preschool children, school-age children, and adolescents; and (3) safety data with a summary of all available

information on the safety of the drug in pediatric patients. The Written Request allows for four efficacy trial designs (Fig. 2) (Pasquali et al. 2002). Of note, it is not necessary for the dose-ranging trial to show that a certain drug is effective in treating pediatric hypertension in order for its manufacturer to be eligible for exclusivity. However, trial data must be “interpretable,” in accordance with the guidelines, in order for the drug manufacturer to be eligible for patent extension. Conducting these trials is further complicated by ethical and methodologic issues unique to pediatric research, in addition to compliance with the formal guidelines. Here we describe the four types of trial designs with the associated examples of pediatric antihypertensive studies listed in Table 1.

**Trial Design A:** In trial design A, patients are randomized to placebo or one of a few different dosages of the test medication (Fig. 2). After 2 weeks of treatment, the trial is analyzed by examining the slope of the placebo-corrected change in blood pressure from baseline as a function of dosage. A negative slope (i.e., the reduction in blood pressure increases as treatment dosage increases) indicates that the trial was successful or that the test drug was effective. If the

**Table 1** Antihypertensive drugs studied under and FDA-issued Written Request

Drug	Trial design	Sample size	Dose response	Label change
Amlodipine	C	268	No	Yes
Benazepril	D	107	No	Yes
Bisoprolol	A	94	Yes	No
Candesartan	A	240	Yes age 1–5/no age 6–17	Yes
Enalapril	C	110	Yes	Yes
Eplerenone	C	304	No	Yes (negative)
Felodipine	D	133	No	No
Fosinopril	C	253	No	Yes
Irbesartan	C	318	No	Yes (negative)
Lisinopril	C	115	Yes	Yes
Losartan	C	175	Yes	Yes
Metoprolol	A	140	No	Yes
Quinapril	A	112	No	No
Ramipril	D	219	No	No
Valsartan	C	351	Yes age 1–5/no age 6–16	Yes
Olmесartan	C	302	Yes	Yes
Sodium nitroprusside	D	63	Yes	Yes

slope were not different from zero, the trial is considered a failure. The major advantage of this trial type is its straightforward design and analysis. Both successful and unsuccessful (“failed”) trials are considered to be interpretable and therefore responsive to the Written Request, so the sponsor is eligible for the additional 6 months of exclusivity.

However, the placebo-controlled design can lead to slow recruitment because parents and physicians are often uncomfortable with the possibility that the child may be placed on placebo. While these trials can employ a 3:1 randomization scheme (thereby three times as many children receive active product), some parents will still have significant concerns about their child’s participation, especially if the trial drug is available off-label. This concern does not appear to be influenced by the fact that in most trials, patients receive standard non-pharmacologic therapy of diet and exercise in all arms of the study. Some have questioned the ethics of conducting placebo-controlled trials in children in general due to the potential risk of adverse events while not on active therapy (Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations 1995; Flynn 2003). We evaluated adverse events in subjects while on placebo in

ten antihypertensive trials and observed no differences in the rates of adverse events reported between the patients who received placebo and those who received active drug. Short-term exposure to placebo in pediatric trials of antihypertensive medications thus appears to be safe (Smith et al. 2008).

**Trial Design B:** To avoid the issues associated with a placebo-controlled trial, trial design B involves randomization to one of two or three dosages of the test medication as in trial design A, but without a placebo arm (Fig. 2). If analysis of trial B reveals a negative slope of the dose-response curve, the trial is considered successful and responsive to the Written Request. However, if the slope were zero, it would not be possible to determine whether this was due to the absence of an effect or if all doses were too low or too high. Therefore, the trial would be considered not only a failure but also uninterpretable. Thus, a negative trial would be unresponsive to the Written Request, and the manufacturer would not be eligible for patent extension. This trial has the simplest design of the four and avoids ethical and patient recruitment issues associated with placebo-controlled trials in children. However, it involves significant risk for manufacturers compared with the other trials, in that only a positive



outcome is considered responsive to the Written Request. More important, the ethics of enrolling pediatric patients in a trial in which the outcome may not be interpretable are questionable and may not provide needed information to physicians caring for such patients. Finally, the lack of controls does not allow adequate assessment of safety. Perhaps for all these reasons, trial design B has not been used in previous pediatric antihypertensive studies (Table 1).

**Trial Design C:** Trial design C employs a more complicated design in order to avoid use of a true placebo arm as in trial design B while adding the power to obtain interpretable results regardless of the outcome of the trial, as in trial design A (Fig. 2). Trial C begins like trial B with randomization to one of three dosages of the test product. In addition, it includes a randomized withdrawal phase. At the end of the treatment period, patients are re-randomized to continue on their assigned treatments or to be withdrawn to placebo, with close follow-up and withdrawal to open-label treatment.

The analysis of the treatment phase is similar to that of trial B. If the slope of the dose-response curve is negative, the trial is considered successful and responsive to the Written Request. However, if the slope is zero during the treatment phase, the addition of the withdrawal phase allows further analysis and interpretation of the trial. For example, if the treatment phase dose-response curve slope was zero but the withdrawal phase demonstrated a rise in blood pressure with withdrawal to placebo, this indicates that the dosages used during the treatment phase were too high. If blood pressure did not change significantly with withdrawal to placebo, this suggests that all dosages were too low, that the withdrawal period was too short to completely wash out the effect of a long-lasting agent, or that the drug was ineffective. Thus, as in trial A, the trial would be considered interpretable regardless of the outcome and, therefore, responsive to the Written Request. Eligibility for exclusivity regardless of outcome is a major advantage of this trial design. In addition, avoiding the use of an explicit placebo arm likely makes this type of trial more appealing when presented to parents.

**Trial Design D:** In design D, the entire trial is built around randomized drug withdrawal (Fig. 2). In this trial, patients are force titrated to maximal tolerated dosages of the drug and then randomly withdrawn to lower dosages, including placebo, with close follow-up, and discretionary withdrawal to open-label therapy. The analysis of this type of trial is similar to that of trial design C. Much like trial C, trial D avoids the use of a placebo arm and is interpretable regardless of outcome. However, the close follow-up and risk of adverse events that come with titration to maximal dosages are considerable disadvantages and can result in recruitment problems.

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## Written Request Criteria

In addition to specifying trial design, the FDA Written Request contains the required elements of the requested studies, including indication, number of studies, sample sizes, trial design, and age ranges required to affect a labeling change. These criteria have undergone several amendments aimed at improving trial standards and ensuring a meaningful and generalizable trial outcome. Written Request criteria generally include:

1. Demographic criteria:
  - (a) Trials are generally expected to include at least 50% preadolescent patients (<Tanner stage 3) as data from prior adult trials is more generalizable to adolescents than to younger children. The most recent Written Request amendment requires that trials enroll  $\geq 200$  subjects ages 6–16 years and  $\geq 50$  subjects ages 1–5 years.
  - (b) Trials are expected to include a mixture of black and non-black patients, with a requirement of 40–60% black subjects.
  - (c) Trials are expected to include patients of both sexes.
2. Inclusion criteria:
  - (a) Hypertension is defined as  $\geq 95\%$  for age/gender/height or  $\geq 90\%$  if concurrent conditions are present, based on “The fourth report on the diagnosis,

evaluation, and treatment of high blood pressure in children and adolescents.”

3. Formulation criteria:

- (a) Trials are expected to use age appropriate formulations. Failure to do so has been an important contributor to prior trial failures (see “use of a liquid formulation” section below). Trial sponsors must make a reasonable attempt to develop a commercially marketable formulation. If attempts fail then the sponsor must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. The sponsor must document attempts and reasons attempts failed. If the reasons are accepted and studies are conducted with a compounded formulation, then the product label must include detailed compounding information.

4. Dose range:

- (a) The dosages chosen should result in blood levels that range from less than those achieved with the lowest approved adult dose to more than those achieved by the highest generally used adult dose. Inappropriate dose ranges has been an important contributor to non-interpretable trials (see below). However, in the past, using doses exceeding those approved for adult patients has been a source of controversy with ethics committees. Existing data from antihypertensive trials in children have lessened these concerns.

5. Endpoint criteria:

- (a) Recommended duration for a dose-ranging trial is typically 2 weeks but possibly longer if a period of dose titration is needed.
- (b) The primary endpoint must be either absolute or percentage change in systolic or diastolic blood pressure. For trial designs A and B, the efficacy measurement should be changed from baseline to the end of the treatment period plus the inter-dosing interval (trough), while for trial designs C and D, the primary efficacy measurement should be changed in

blood pressure from the last on-treatment visit to the end of the withdrawal period. The length of time of the withdrawal period should be adequate to ensure the return of blood pressure to pretreatment levels. Withdrawal timing can be best estimated from the drug half-life determined in pharmacokinetic studies conducted in both adults and children.

- (c) For pharmacokinetic trials, traditional or sparse sampling can be chosen, although sparse sampling may be more difficult for a newer agent without an existing user group. For the parent and each metabolite, trials should estimate bioavailability (AUC) half-life,  $C_{max}$ , and  $T_{max}$  in the various age groups. These studies should be done prior to the clinical trial so that the data can inform dose selection and dosing intervals.

It should be noted that endpoint criteria in pediatric trials (i.e., systolic or diastolic blood pressure reduction) are used as surrogate markers of cardiovascular disease. This differs from the typical endpoint criteria used in many adult hypertension trials where “hard” endpoints like mortality, stroke, or myocardial infarction are more common and therefore more feasible as trial endpoints.

6. Safety criteria:

- (a) Trials should follow patients at least weekly for adverse events and to detect unacceptable increases in blood pressure.
- (b) Trials should include an independent Data Safety and Monitoring Committee (DSMC).
- (c) Trials should include a 1-year open-label treatment period to evaluate all available information published and unpublished and to include information on adverse events, growth (change in head circumference, weight, length, or height), and development (milestones, school performance, neurocognitive testing).

7. Statistical considerations:

- (a) Trials should have at least 80% power to detect a 3 mmHg change in blood

pressure of conventional ( $p < 0.05$ , two-sided) statistical significance.

- (b) Interim analyses are typically allowed in order to assess variability following a prespecified rule to adjust the sample size to achieve the specified target power. Interim analysis must be performed at  $>90\%$  of initially planned enrollment. Options for estimating variability are (1) a blinded, pooled analysis of all groups, (2) a blinded analysis of one group, or (3) a partially unblinded analysis of variability within each group (performed by an independent third party). No alpha-spending adjustment is required for the interim analysis, but if an efficacy assessment is performed at this or some other interim analysis, an appropriate alpha adjustment is required.

#### 8. Reporting criteria:

- (a) The Written Request and medical, statistical, and clinical pharmacology reviews must be posted on the FDA website.
- (b) Trials should be registered on ClinicalTrials.gov (required by legislation).

## Clinical Efficacy Studies

The passage of the Food and Drug Administration Modernization Act in 1997 has been the single greatest stimulus for the recent proliferation of industry-sponsored trials of antihypertensive agents in children (Flynn and Daniels 2006). Table 1 lists the various studies completed to date, and Fig. 1 provides a timeline of antihypertensive drugs that have been studied and subsequently granted a new pediatric indication in the United States. The results of many, but not all, of the clinical trials of antihypertensive agents in children have resulted in publications in scientific journals (Batisky et al. 2007; Benjamin et al. 2008; Blumer et al. 2003; Flynn et al. 2004, 2008; Hammer et al. 2015; Hazan et al. 2010; Li et al. 2004, 2010; Meyers et al. 2011; Sakarcin et al. 2001; Schaefer et al. 2010, 2011; Shahinfar et al. 2005; Soffer et al. 2003; Sorof et al. 2002a;

Trachtman et al. 2003, 2008; Wells et al. 2002, 2010, 2011). Furthermore, the Best Pharmaceuticals for Children Act now requires the FDA to publish the results of its internal analyses of the trial results submitted by sponsors on the Internet (U.S. Food and Drug Administration 2016b). The reauthorization of 2012 requires the FDA to release on its website certain data reviews of BPCA studies submitted between 2002 and 2007 that have never been made publicly available.

Several recent reviews summarize the advances in our knowledge about the use of antihypertensive agents in children and provide updated recommendations on the optimal use of antihypertensive agents in children and adolescents who require pharmacologic treatment (Blowey 2012; Ferguson and Flynn 2014; Flynn and Daniels 2006). Of note, however, many studies failed to show a dose response. As a pattern of failed pediatric antihypertensive trials emerged, we sought to determine why these trials failed to show dose response in children and hypothesized that difficulties in dosing might be the cause of trial failure (Benjamin et al. 2008). Using meta-analytic techniques, we determined that several factors are important which were predictive of trial success. These factors are discussed below.

**Dose Range:** The dose range received by children randomly assigned to low- and high-dosage groups is extremely variable between trials. For example, in the amlodipine trial (Flynn et al. 2004) (which failed), there was a twofold difference between the high-dosage and low-dosage groups: children in the high-dosage group received 5 mg and children in the low-dosage group received 2.5 mg. In the fosinopril (Li et al. 2004) and irbesartan trials (Sakarcin et al. 2001) (which also failed), dosing ranges were also small, at six- and ninefold, respectively. The enalapril (Wells et al. 2002), lisinopril (Soffer et al. 2003), and losartan (Shahinfar et al. 2005) trials (which were successful in demonstrating a dose response) had considerably higher dosing ranges, at 32-fold, 32-fold, and 20-fold, respectively. The successful trials thus incorporated a wide range of doses. The lowest clinical trial dose should be lower than the lowest approved dose in adults, and the highest clinical trial dose should at least be twofold higher

than the highest approved dose in adults, unless contraindicated for safety concerns.

None of the failed trials investigated dose ranges higher than the corresponding adult doses. For example, the highest irbesartan dosage was 2 mg/kg (Sakarcan et al. 2001), whereas adult data indicate that most adults need dosages up to 150–300 mg (~2 to 4 mg/kg for a 75-kg child) for better blood pressure control. Data obtained from irbesartan use in adults showed that effects on blood pressure increase at dosages  $\geq 600$  mg (~8 mg/kg for a 75-kg child) and the maximum irbesartan dosage studied in adults was 900 mg.

In contrast, successful trials provided large differences across low-, medium-, and high-dosage strata. Successful trials used dosages much lower (nearly placebo) than the dosages approved in adults. For example, the recommended initial lisinopril dose in adults is 10 mg, and the usual dose range is 20–40 mg. The lowest dosage used in the pediatric clinical trial was 0.625 mg, thus providing a wider range for exploring dose response (Soffer et al. 2003).

The selection of wide dosage ranges has important pharmacokinetic/pharmacodynamic implications because closely spaced dosages will likely yield overlapping exposures among dose groups. If overlap is substantial, the dose response could appear flat and, thus, fail to demonstrate a significant dose response relationship.

**Dose by Weight:** Weight-based dosing strategies were inconsistent in the trials. The amlodipine trial did not incorporate individual subject weight in dosing but rather gave all children in the low-dosage arm 2.5 mg of product and all children in the high-dosage arm 5 mg of product. This dosing strategy resulted in the following paradox: a 100-kg subject randomly assigned to “high” dosage received 0.05 mg/kg, and a 20-kg subject randomly assigned to “low” dosage received 0.125 mg/kg. In the low-dosage group, one fourth of subjects received  $>0.06$  mg/kg, and one fourth of the high-dosage group received  $<0.06$  mg/kg. Although blood pressure did not show a dose response to amlodipine as randomized, increased dosage on a milligram per kilogram basis was associated with a decrease in blood pressure (Flynn et al. 2012).

The fosinopril trial also failed to demonstrate a dose response, although it incorporated individual subject weight into the dosing (Li et al. 2004). However, the weight-based strategy of dosing in this trial was limited in that no child received a dosage  $>40$  mg. Thus, children randomly assigned to medium dosage who weighed  $<30$  kg received more fosinopril (in milligrams per kilogram) than the heaviest subjects randomly assigned to high dosage. Similar to the amlodipine trial, blood pressure dose response was not associated with product as randomized, but increased dosing on a milligrams per kilogram basis was associated with blood pressure reduction.

**Development and Use of a Liquid Formulation:** Several of the trials of orally administered antihypertensive agents (particularly those used in the failed trials) did not develop a pediatric (e.g., liquid) formulation and, thus, exhibited a wide range in exposure within each weight stratum. This is because precise dosing is not feasible using a limited number of tablets; liquid formulations allow for more precise dosing per kilogram. Development of a liquid formulation is often challenging because bioavailability can be unreliable, and dissolving some agents in liquid can require high concentrations of alcohol, which would not be acceptable for administration to children. In addition, stability and bioequivalence testing of liquid formulations also require additional time and expense. Moreover, it is important that the liquid formulation be palatable, and often crushed tablets suspended in an aqueous medium are bitter tasting, which ultimately will affect drug compliance. As a result of these issues, pediatric formulations are now required by the FDA Written Request (see requirements outlined above). Bioequivalence studies of the pediatric formulation with the adult formulation must be performed but can be performed in adult subjects. Additionally, acceptability testing of the pediatric formulations in hypertensive children must be performed to ensure the formulation will be palatable in flavor, form, and taste.

**Primary Endpoint:** Most successful trials used change in diastolic blood pressure as the primary endpoint. To some extent success of these trials might have been related to a higher

incidence of secondary hypertension in those with diastolic hypertension. Therefore, the underlying etiology (i.e., renal disease) may be concomitantly treated by the trial drug. However, it is also likely that use of diastolic blood pressure as the primary endpoint contributed to the trial success as most unsuccessful studies (e.g., trials of amlodipine, fosinopril, and irbesartan) used change in sitting systolic blood pressure as the primary outcome. We evaluated the reduction in systolic and diastolic blood pressures related to several agents and found that a reduction in diastolic blood pressure was more closely related to the dosage of agent administered. For example, in the enalapril trial, the dosage was more closely related to a reduction in diastolic blood pressure than systolic blood pressure (coefficient 0.19 [ $P = 0.001$ ] versus coefficient 0.12;  $P = 0.08$ ). We also observed a closer relationship between diastolic blood pressure reduction and dosage in the lisinopril trial (coefficient 0.12 [ $P = 0.001$ ] versus coefficient 0.08;  $P = 0.09$ ) (Benjamin et al. 2008).

The reason for this closer relationship between diastolic blood pressure reduction and dosage likely relates to the fact that there is less variability associated with measurement of diastolic blood pressure compared to systolic blood pressure. Diastolic blood pressure has less physiological variability among observations within a subject than systolic blood pressure in children. This reduction in variability may contribute to the success of diastolic blood pressure as the primary endpoint. Systolic hypertension is however more than threefold more common than diastolic hypertension in children and adolescents, and the motivation to use systolic blood pressure as the primary endpoint derives from feasibility, a common problem in conducting pediatric drug trials (Flynn and Alderman 2005; Sorof et al. 2002b). A primary study endpoint of mean arterial blood pressure that incorporates both systolic and diastolic blood pressure values might prove advantageous, and this possibility should be explored in future trials.

**Blood Pressure Measurement:** There is heterogeneity in methodology used to measure blood pressure for clinical trials. Some trials have relied on oscillometric devices (Flynn et al. 2004; Li et al. 2004, 2010; Sakarcan et al. 2001), while

others used auscultation (Batiscky et al. 2007; Hazan et al. 2010; Shahinfar et al. 2005; Sorof et al. 2002a; Trachtman et al. 2003, 2008; Wells et al. 2002, 2010, 2011). Even more complicated, the device used for blood pressure measurement was not specified in the trial design for some studies, and both auscultation and oscillometric devices were used based on individual site preference (Flynn et al. 2008). The two methods do not always agree, and significant differences have been detected in certain patient populations (Flynn et al. 2012; Skirton et al. 2011). Auscultation is considered the gold standard for direct measurement of systolic and diastolic blood pressure and is recommended as the preferred method of blood pressure measurement in children (The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents 2004). Oscillometric devices directly measure mean arterial pressure and then compute systolic and diastolic pressures using an algorithm. Potentially these devices might be best used in clinical trials for assessment of mean arterial pressure, although this has not been specifically studied. Regardless of the device used, it should be specified within the trial design to ensure consistent methodology among study sites.

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## Conclusion

As a result of legislative incentives, much has been learned about the treatment of hypertension in children and adolescents in the last decade. This expansion of our knowledge base allows for improved understanding of efficacy and safety of these agents. Understanding clinical trial design in pediatric studies is paramount: poor dose selection, failure to fully incorporate weight and pediatric pharmacology into trial design, lack of liquid formulation development, and use of systolic blood pressure as the primary endpoint likely led to the failure of several antihypertensive pediatric exclusivity trials. These data and trial experiences over the preceding decade have already resulted in changes to the FDA Written Request template that will improve trial design in children and adolescents. In the future, we recommend that

pediatric antihypertensive trials do the following: (1) develop an exposure-response model using adult data and published pediatric data and use this model to perform clinical trial simulations of pediatric studies and to explore competing trial designs and analysis options, (2) work with the FDA to design pediatric trials by leveraging previous quantitative knowledge, and (3) routinely collect blood samples at informative time points to assess the pharmacokinetics in each subject to ascertain exposure response analysis. In addition, studies of the comparative effectiveness, long-term safety, and effects on growth and development are needed. Additional studies might also explore effects on vascular reactivity and the impact of pharmacologic treatment on outcomes such as development of cardiovascular morbidity and mortality.

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## Cross-References

- ▶ Cohort Studies, Meta-analyses, and Clinical Trials in Childhood Hypertension
- ▶ Diagnostic Evaluation of Pediatric Hypertension
- ▶ Pharmacologic Treatment of Pediatric Hypertension

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## Correction to: Pharmacologic Treatment of Pediatric Hypertension

Michael A. Ferguson

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### Correction to:

**Chapter 44 in: J.T. Flynn et al. (eds.), *Pediatric Hypertension*,  
[https://doi.org/10.1007/978-3-319-31107-4\\_36](https://doi.org/10.1007/978-3-319-31107-4_36)**

The book was inadvertently published with incorrect text in Table 3. The text has been corrected in the table to read as follows:

The maximum dose for Captopril is 6 mg/kg/day.

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# Appendix: Highlights of the 2017 American Academy of Pediatrics Clinical Practice Guideline for the Screening and Management of High Blood Pressure in Children and Adolescents

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## Introduction

As has been described elsewhere (Flynn and Falkner 2009), hypertension (HTN) in children and adolescents was first investigated in the 1960s and 1970s by a small group of investigators. These early studies highlighted uncertainty in several areas, beginning with the criteria for the diagnosis of HTN in pediatric patients. In response, the National High Blood Pressure Education Program (NHBEP) of the National Heart Lung and Blood Institute (NHLBI) convened a Task Force to address the following issues:

- Proper blood pressure (BP) measurement techniques for use in children and adolescents
- Distribution of normal BP values in children and adolescents and determination of the upper limits of normal BP according to age
- Diagnostic evaluation of the child or adolescent with elevated BP
- Management of the child or adolescent who has received the diagnosis of HTN
- Prediction of the long-term outcomes of primary HTN in childhood

The report of that NHBEP Task Force (Blumenthal et al. 1977) constituted the first clinical practice guideline (CPG) for childhood HTN. Major updates were published in 1987, 1996, and 2004 (Task Force on Blood Pressure Control in Children 1987; NHBPEP Working Group 1996; NHBPEP Working Group 2004). Minor updates of antihypertensive drug dosing for children, but no new recommendations related to evaluation or management of high childhood BP, were incorporated into the 2011 NHLBI Integrated guideline on pediatric cardiovascular health (NHLBI 2011).

Since publication of the 2004 Fourth Report, there has been increased interest in the problem of childhood hypertension, with many new studies addressing the epidemiology, treatment and outcome of high BP in the young. Much of this interest has been fueled by the growing pediatric obesity epidemic and also by legislative initiatives designed to increase the number of drug studies conducted in children and adolescents with various health conditions, among them HTN (see ► Chap. 38, “Changes in Drug Development Regulations and Their Impact on Clinical Trials”). In the early 2010s, several prominent investigators in the field of pediatric HTN began developing the case for an updated pediatric HTN guideline with the intent of approaching the NHLBI for support. However, the 2013 announcement by the NHLBI (Gibbons et al. 2013) that it would no longer sponsor the development of new CPGs itself prompted this group to approach the American Academy of Pediatrics (AAP) to sponsor development

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of a new pediatric HTN CPG, which it agreed to do in early 2014.

The 2017 AAP CPG (Flynn et al. 2017) was developed using a rigorous evidence-based approach as recommended by the Institute of Medicine (2011). Four primary patient-intervention-comparison-outcome-treatment (PICOT) questions were generated. These PICOT questions were used to carry out a systematic review of the literature on childhood HTN published between January 2004 and July 2016. References so identified were reviewed, assessed for quality and relevance, and then used to generate 30 “Key Action Statements (KAS),” all of which were graded based on the strength of the available evidence. Such methodology represents a departure from the approach used in the prior NHBPEP pediatric HTN guidelines, but is consistent with the more recent recommendations from the NHLBI regarding development of CPGs for cardiovascular disease (Gibbons et al. 2013). There are also an additional 27 clinical recommendations in the new CPG that are based on the expert opinion of the AAP Subcommittee that developed the CPG on issues for which insufficient evidence was available to generate KASs.

In this appendix, we present a brief summary of the major points covered in the new CPG, with an emphasis on recommendations that have changed substantially since publication of the 2004 Fourth Report (NHBPEP Working Group 2004). The interested reader should consult the full AAP CPG (Flynn et al. 2017), which contains additional tables, figures, and supporting information designed to assist the clinician in evaluating and managing children and adolescents with HTN.

## Definition of Hypertension and Blood Pressure Tables

Three important features of the 2017 AAP CPG include a revision of the definition of HTN in children and adolescents, development of new normative tables for childhood blood pressure (Tables 1 and 2), and inclusion of a “simplified” BP table for screening purposes (Table 3). Recognizing that there still are no cardiovascular outcome

data that can be used to define a single BP level to consider as “hypertensive” in the pediatric age group, the AAP Subcommittee adopted a statistical definition of childhood HTN similar to that used in the prior NHBPEP reports with two changes: (1) replacement of the term “prehypertension” with “elevated BP” for BP values  $\geq 90$ th percentile but  $< 95$ th percentile and (2) adoption of adult BP cut-points to define abnormal BP levels in adolescents  $\geq 13$  years of age (the BP value used to denote stage 2 HTN has also been changed to BP  $> 95$ th percentile +12 mmHg). These two changes were made to align with terminology and BP cut-points in a new CPG for adult HTN being issued by the American College of Cardiology (ACC) and American Heart Association (AHA) and also to make management of hypertensive adolescents more straightforward.

The revised HTN definitions and BP staging/classification system can be summarized as follows:

- **Normal BP:** BP  $< 90$ th percentile for age, sex, and height; or  $< 120 / < 80$  mmHg for adolescents  $\geq 13$  years old
- **Elevated BP:** BP reading  $\geq 90$ th percentile and  $< 95$ th percentile for age, sex, and height; or  $120\text{--}129 / < 80$  mmHg for adolescents  $\geq 13$  years old
- **Hypertension:** BP  $> 95$ th percentile for age, sex, and height; or  $\geq 130 / 80$  mmHg for adolescents  $\geq 13$  years old. Hypertensive-level BP is further staged as follows:
  - **Stage 1 hypertension:** BP  $> 95$ th percentile for age, sex, and height up to the 95th percentile +11 mmHg; or  $130\text{--}139 / 80\text{--}89$  mmHg for adolescents  $\geq 13$  years of age
  - **Stage 2 hypertension:** BP  $\geq 95$ th percentile +12 mmHg for age, sex, and height; or  $> 140 / 90$  mmHg for adolescents  $\geq 13$  years of age

Many have found the BP tables in the 2004 Fourth Report (NHBPEP Working Group 2004) difficult to use and have blamed those tables for resultant under-recognition of childhood HTN (Mitchell et al. 2011). Additionally, the NHBPEP database used to generate the BP values

contained a large number of overweight and obese children from the 1999–2000 National Health and Nutrition Examination Survey (NHANES), potentially leading to higher BP values, given the known effects of obesity on BP. Indeed, a reanalysis of the

NHBPEP database in 2008 demonstrated that exclusion of overweight and obese children resulted in BP values that were on average 2–3 mmHg lower than those in the 2004 Fourth Report (Rosner et al. 2008). Given this, the AAP

**Table 1** BP levels for boys by age and height percentile

Age (years)	BP Percentile	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		Height percentile or measured height							Height percentile or measured height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
1	Height-inches	30.4	30.8	31.6	32.4	33.3	34.1	34.6	30.4	30.8	31.6	32.4	33.3	34.1	34.6
	Height-cm	77.2	78.3	80.2	82.4	84.6	86.7	87.9	77.2	78.3	80.2	82.4	84.6	86.7	87.9
	50th	85	85	86	86	87	88	88	40	40	40	41	41	42	42
	90th	98	99	99	100	100	101	101	52	52	53	53	54	54	54
	95th	102	102	103	103	104	105	105	54	54	55	55	56	57	57
	95th +12 mmHg	114	114	115	115	116	117	117	66	66	67	67	68	69	69
2	Height-inches	33.9	34.4	35.3	36.3	37.3	38.2	38.8	33.9	34.4	35.3	36.3	37.3	38.2	38.8
	Height-cm	86.1	87.4	89.6	92.1	94.7	97.1	98.5	86.1	87.4	89.6	92.1	94.7	97.1	98.5
	50th	87	87	88	89	89	90	91	43	43	44	44	45	46	46
	90th	100	100	101	102	103	103	104	55	55	56	56	57	58	58
	95th	104	105	105	106	107	107	108	57	58	58	59	60	61	61
	95th +12 mmHg	116	117	117	118	119	119	120	69	70	70	71	72	73	73
3	Height-inches	36.4	37	37.9	39	40.1	41.1	41.7	36.4	37	37.9	39	40.1	41.1	41.7
	Height-cm	92.5	93.9	96.3	99	101.8	104.3	105.8	92.5	93.9	96.3	99	101.8	104.3	105.8
	50th	88	89	89	90	91	92	92	45	46	46	47	48	49	49
	90th	101	102	102	103	104	105	105	58	58	59	59	60	61	61
	95th	106	106	107	107	108	109	109	60	61	61	62	63	64	64
	95th +12 mmHg	118	118	119	119	120	121	121	72	73	73	74	75	76	76
4	Height-inches	38.8	39.4	40.5	41.7	42.9	43.9	44.5	38.8	39.4	40.5	41.7	42.9	43.9	44.5
	Height-cm	98.5	100.2	102.9	105.9	108.9	111.5	113.2	98.5	100.2	102.9	105.9	108.9	111.5	113.2
	50th	90	90	91	92	93	94	94	48	49	49	50	51	52	52
	90th	102	103	104	105	105	106	107	60	61	62	62	63	64	64
	95th	107	107	108	108	109	110	110	63	64	65	66	67	67	68
	95th +12 mmHg	119	119	120	120	121	122	122	75	76	77	78	79	79	80
5	Height-inches	41.1	41.8	43.0	44.3	45.5	46.7	47.4	41.1	41.8	43.0	44.3	45.5	46.7	47.4
	Height-cm	104.4	106.2	109.1	112.4	115.7	118.6	120.3	104.4	106.2	109.1	112.4	115.7	118.6	120.3
	50th	91	92	93	94	95	96	96	51	51	52	53	54	55	55
	90th	103	104	105	106	107	108	108	63	64	65	65	66	67	67
	95th	107	108	109	109	110	111	112	66	67	68	69	70	70	71
	95th +12 mmHg	119	120	121	121	122	123	124	78	79	80	81	82	82	83
6	Height-inches	43.4	44.2	45.4	46.8	48.2	49.4	50.2	43.4	44.2	45.4	46.8	48.2	49.4	50.2
	Height-cm	110.3	112.2	115.3	118.9	122.4	125.6	127.5	110.3	112.2	115.3	118.9	122.4	125.6	127.5
	50th	93	93	94	95	96	97	98	54	54	55	56	57	57	58
	90th	105	105	106	107	109	110	110	66	66	67	68	68	69	69

(continued)

**Table 1** (continued)

	95th	108	109	110	111	112	113	114	69	70	70	71	72	72	73
	95th +12 mmHg	120	121	122	123	124	125	126	81	82	82	83	84	84	85
7	Height-inches	45.7	46.5	47.8	49.3	50.8	52.1	52.9	45.7	46.5	47.8	49.3	50.8	52.1	52.9
	Height-cm	116.1	118	121.4	125.1	128.9	132.4	134.5	116.1	118	121.4	125.1	128.9	132.4	134.5
	50th	94	94	95	97	98	98	99	56	56	57	58	58	59	59
	90th	106	107	108	109	110	111	111	68	68	69	70	70	71	71
	95th	110	110	111	112	114	115	116	71	71	72	73	73	74	74
	95th +12 mmHg	122	122	123	124	126	127	128	83	83	84	85	85	86	86
8	Height-inches	47.8	48.6	50	51.6	53.2	54.6	55.5	47.8	48.6	50	51.6	53.2	54.6	55.5
	Height-cm	121.4	123.5	127	131	135.1	138.8	141	121.4	123.5	127	131	135.1	138.8	141
	50th	95	96	97	98	99	99	100	57	57	58	59	59	60	60
	90th	107	108	109	110	111	112	112	69	70	70	71	72	72	73
	95th	111	112	112	114	115	116	117	72	73	73	74	75	75	75
	95th +12 mmHg	123	124	124	126	127	128	129	84	85	85	86	87	87	87
9	Height-inches	49.6	50.5	52	53.7	55.4	56.9	57.9	49.6	50.5	52	53.7	55.4	56.9	57.9
	Height-cm	126	128.3	132.1	136.3	140.7	144.7	147.1	126	128.3	132.1	136.3	140.7	144.7	147.1
	50th	96	97	98	99	100	101	101	57	58	59	60	61	62	62
	90th	107	108	109	110	112	113	114	70	71	72	73	74	74	74
	95th	112	112	113	115	116	118	119	74	74	75	76	76	77	77
	95th +12 mmHg	124	124	125	127	128	130	131	86	86	87	88	88	89	89
10	Height-inches	51.3	52.2	53.8	55.6	57.4	59.1	60.1	51.3	52.2	53.8	55.6	57.4	59.1	60.1
	Height-cm	130.2	132.7	136.7	141.3	145.9	150.1	152.7	130.2	132.7	136.7	141.3	145.9	150.1	152.7
	50th	97	98	99	100	101	102	103	59	60	61	62	63	63	64
	90th	108	109	111	112	113	115	116	72	73	74	74	75	75	76
	95th	112	113	114	116	118	120	121	76	76	77	77	78	78	78
	95th +12 mmHg	124	125	126	128	130	132	133	88	88	89	89	90	90	90
11	Height-inches	53	54	55.7	57.6	59.6	61.3	62.4	53	54	55.7	57.6	59.6	61.3	62.4
	Height-cm	134.7	137.3	141.5	146.4	151.3	155.8	158.6	134.7	137.3	141.5	146.4	151.3	155.8	158.6
	50th	99	99	101	102	103	104	106	61	61	62	63	63	63	63
	90th	110	111	112	114	116	117	118	74	74	75	75	75	76	76
	95th	114	114	116	118	120	123	124	77	78	78	78	78	78	78
	95th +12 mmHg	126	126	128	130	132	135	136	89	90	90	90	90	90	90
12	Height-inches	55.2	56.3	58.1	60.1	62.2	64	65.2	55.2	56.3	58.1	60.1	62.2	64	65.2
	Height-cm	140.3	143	147.5	152.7	157.9	162.6	165.5	140.3	143	147.5	152.7	157.9	162.6	165.5
	50th	101	101	102	104	106	108	109	61	62	62	62	62	63	63
	90th	113	114	115	117	119	121	122	75	75	75	75	75	76	76
	95th	116	117	118	121	124	126	128	78	78	78	78	78	79	79
	95th +12 mmHg	128	129	130	133	136	138	140	90	90	90	90	90	91	91

(continued)

**Table 1** (continued)

13	Height-inches	57.9	59.1	61	63.1	65.2	67.1	68.3	57.9	59.1	61	63.1	65.2	67.1	68.3
	Height-cm	147	150	154.9	160.3	165.7	170.5	173.4	147	150	154.9	160.3	165.7	170.5	173.4
	50th	103	104	105	108	110	111	112	61	60	61	62	63	64	65
	90th	115	116	118	121	124	126	126	74	74	74	75	76	77	77
	95th	119	120	122	125	128	130	131	78	78	78	78	80	81	81
	95th +12 mmHg	131	132	134	137	140	142	143	90	90	90	90	92	93	93
14	Height-inches	60.6	61.8	63.8	65.9	68.0	69.8	70.9	60.6	61.8	63.8	65.9	68.0	69.8	70.9
	Height-cm	153.8	156.9	162	167.5	172.7	177.4	180.1	153.8	156.9	162	167.5	172.7	177.4	180.1
	50th	105	106	109	111	112	113	113	60	60	62	64	65	66	67
	90th	119	120	123	126	127	128	129	74	74	75	77	78	79	80
	95th	123	125	127	130	132	133	134	77	78	79	81	82	83	84
	95th +12 mmHg	135	137	139	142	144	145	146	89	90	91	93	94	95	96
15	Height-inches	62.6	63.8	65.7	67.8	69.8	71.5	72.5	62.6	63.8	65.7	67.8	69.8	71.5	72.5
	Height-cm	159	162	166.9	172.2	177.2	181.6	184.2	159	162	166.9	172.2	177.2	181.6	184.2
	50th	108	110	112	113	114	114	114	61	62	64	65	66	67	68
	90th	123	124	126	128	129	130	130	75	76	78	79	80	81	81
	95th	127	129	131	132	134	135	135	78	79	81	83	84	85	85
	95th +12 mmHg	139	141	143	144	146	147	147	90	91	93	95	96	97	97
16	Height-inches	63.8	64.9	66.8	68.8	70.7	72.4	73.4	63.8	64.9	66.8	68.8	70.7	72.4	73.4
	Height-cm	162.1	165	169.6	174.6	179.5	183.8	186.4	162.1	165	169.6	174.6	179.5	183.8	186.4
	50th	111	112	114	115	115	116	116	63	64	66	67	68	69	69
	90th	126	127	128	129	131	131	132	77	78	79	80	81	82	82
	95th	130	131	133	134	135	136	137	80	81	83	84	85	86	86
	95th +12 mmHg	142	143	145	146	147	148	149	92	93	95	96	97	98	98
17	Height-inches	64.5	65.5	67.3	69.2	71.1	72.8	73.8	64.5	65.5	67.3	69.2	71.1	72.8	73.8
	Height-cm	163.8	166.5	170.9	175.8	180.7	184.9	187.5	163.8	166.5	170.9	175.8	180.7	184.9	187.5
	50th	114	115	116	117	117	118	118	65	66	67	68	69	70	70
	90th	128	129	130	131	132	133	134	78	79	80	81	82	82	83
	95th	132	133	134	135	137	138	138	81	82	84	85	86	86	87
	95th +12 mmHg	144	145	146	147	149	150	150	93	94	96	97	98	98	99

Use percentile values to stage BP readings according to the scheme in Table 1: Elevated BP:  $\geq 90$ th percentile; stage 1 HTN:  $\geq 95$ th percentile; stage 2 HTN:  $\geq 95$ th percentile +12 mmHg. The 50th, 90th, and 95th percentiles were derived using quantile regression based on normal weight children (BMI percentile  $< 85$ ) (Rosner et al. 2008)

commissioned development of a new set of normative BP values based only on BP measurements obtained in normal-weight children in the NHBPEP database for the new CPG (Tables 1 and 2), and also used those newer results to develop a simplified table of BP values to be used for screening purposes that should prompt

further evaluation (Table 3). A quick glance at the full tables also demonstrates that use of adult BP cut-points for adolescents  $\geq 13$  years of age is appropriate, as 120/80 mmHg, the cut-point for elevated BP in adults, emerges as the 90th percentile at about that age for both boys and girls.

**Table 2** BP levels for girls by age and height percentile

Age (years)	BP Percentile	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		Height percentile or measured height							Height percentile or measured height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
1	Height-inches	29.7	30.2	30.9	31.8	32.7	33.4	33.9	29.7	30.2	30.9	31.8	32.7	33.4	33.9
	Height-cm	75.4	76.6	78.6	80.8	83	84.9	86.1	75.4	76.6	78.6	80.8	83	84.9	86.1
	50th	84	85	86	86	87	88	88	41	42	42	43	44	45	46
	90th	98	99	99	100	101	102	102	54	55	56	56	57	58	58
	95th	101	102	102	103	104	105	105	59	59	60	60	61	62	62
	95th +12 mmHg	113	114	114	115	116	117	117	71	71	72	72	73	74	74
2	Height-inches	33.4	34	34.9	35.9	36.9	37.8	38.4	33.4	34	34.9	35.9	36.9	37.8	38.4
	Height-cm	84.9	86.3	88.6	91.1	93.7	96	97.4	84.9	86.3	88.6	91.1	93.7	96	97.4
	50th	87	87	88	89	90	91	91	45	46	47	48	49	50	51
	90th	101	101	102	103	104	105	106	58	58	59	60	61	62	62
	95th	104	105	106	106	107	108	109	62	63	63	64	65	66	66
	95th +12 mmHg	116	117	118	118	119	120	121	74	75	75	76	77	78	78
3	Height-inches	35.8	36.4	37.3	38.4	39.6	40.6	41.2	35.8	36.4	37.3	38.4	39.6	40.6	41.2
	Height-cm	91	92.4	94.9	97.6	100.5	103.1	104.6	91	92.4	94.9	97.6	100.5	103.1	104.6
	50th	88	89	89	90	91	92	93	48	48	49	50	51	53	53
	90th	102	103	104	104	105	106	107	60	61	61	62	63	64	65
	95th	106	106	107	108	109	110	110	64	65	65	66	67	68	69
	95th +12 mmHg	118	118	119	120	121	122	122	76	77	77	78	79	80	81
4	Height-inches	38.3	38.9	39.9	41.1	42.4	43.5	44.2	38.3	38.9	39.9	41.1	42.4	43.5	44.2
	Height-cm	97.2	98.8	101.4	104.5	107.6	110.5	112.2	97.2	98.8	101.4	104.5	107.6	110.5	112.2
	50th	89	90	91	92	93	94	94	50	51	51	53	54	55	55
	90th	103	104	105	106	107	108	108	62	63	64	65	66	67	67
	95th	107	108	109	109	110	111	112	66	67	68	69	70	70	71
	95th +12 mmHg	119	120	121	121	122	123	124	78	79	80	81	82	82	83
5	Height-inches	40.8	41.5	42.6	43.9	45.2	46.5	47.3	40.8	41.5	42.6	43.9	45.2	46.5	47.3
	Height-cm	103.6	105.3	108.2	111.5	114.9	118.1	120	103.6	105.3	108.2	111.5	114.9	118.1	120
	50th	90	91	92	93	94	95	96	52	52	53	55	56	57	57
	90th	104	105	106	107	108	109	110	64	65	66	67	68	69	70
	95th	108	109	109	110	111	112	113	68	69	70	71	72	73	73
	95th +12 mmHg	120	121	121	122	123	124	125	80	81	82	83	84	85	85
6	Height-inches	43.3	44	45.2	46.6	48.1	49.4	50.3	43.3	44	45.2	46.6	48.1	49.4	50.3
	Height-cm	110	111.8	114.9	118.4	122.1	125.6	127.7	110	111.8	114.9	118.4	122.1	125.6	127.7
	50th	92	92	93	94	96	97	97	54	54	55	56	57	58	59
	90th	105	106	107	108	109	110	111	67	67	68	69	70	71	71

(continued)

**Table 2** (continued)

	95th	109	109	110	111	112	113	114	70	71	72	72	73	74	74
	95th +12 mmHg	121	121	122	123	124	125	126	82	83	84	84	85	86	86
7	Height-inches	45.6	46.4	47.7	49.2	50.7	52.1	53	45.6	46.4	47.7	49.2	50.7	52.1	53
	Height-cm	115.9	117.8	121.1	124.9	128.8	132.5	134.7	115.9	117.8	121.1	124.9	128.8	132.5	134.7
	50th	92	93	94	95	97	98	99	55	55	56	57	58	59	60
	90th	106	106	107	109	110	111	112	68	68	69	70	71	72	72
	95th	109	110	111	112	113	114	115	72	72	73	73	74	74	75
	95th +12 mmHg	121	122	123	124	125	126	127	84	84	85	85	86	86	87
8	Height-inches	47.6	48.4	49.8	51.4	53	54.5	55.5	47.6	48.4	49.8	51.4	53	54.5	55.5
	Height-cm	121	123	126.5	130.6	134.7	138.5	140.9	121	123	126.5	130.6	134.7	138.5	140.9
	50th	93	94	95	97	98	99	100	56	56	57	59	60	61	61
	90th	107	107	108	110	111	112	113	69	70	71	72	72	73	73
	95th	110	111	112	113	115	116	117	72	73	74	74	75	75	75
	95th +12 mmHg	122	123	124	125	127	128	129	84	85	86	86	87	87	87
9	Height-inches	49.3	50.2	51.7	53.4	55.1	56.7	57.7	49.3	50.2	51.7	53.4	55.1	56.7	57.7
	Height-cm	125.3	127.6	131.3	135.6	140.1	144.1	146.6	125.3	127.6	131.3	135.6	140.1	144.1	146.6
	50th	95	95	97	98	99	100	101	57	58	59	60	60	61	61
	90th	108	108	109	111	112	113	114	71	71	72	73	73	73	73
	95th	112	112	113	114	116	117	118	74	74	75	75	75	75	75
	95th +12 mmHg	124	124	125	126	128	129	130	86	86	87	87	87	87	87
10	Height-inches	51.1	52	53.7	55.5	57.4	59.1	60.2	51.1	52	53.7	55.5	57.4	59.1	60.2
	Height-cm	129.7	132.2	136.3	141	145.8	150.2	152.8	129.7	132.2	136.3	141	145.8	150.2	152.8
	50th	96	97	98	99	101	102	103	58	59	59	60	61	61	62
	90th	109	110	111	112	113	115	116	72	73	73	73	73	73	73
	95th	113	114	114	116	117	119	120	75	75	76	76	76	76	76
	95th +12 mmHg	125	126	126	128	129	131	132	87	87	88	88	88	88	88
11	Height-inches	53.4	54.5	56.2	58.2	60.2	61.9	63	53.4	54.5	56.2	58.2	60.2	61.9	63
	Height-cm	135.6	138.3	142.8	147.8	152.8	157.3	160	135.6	138.3	142.8	147.8	152.8	157.3	160
	50th	98	99	101	102	104	105	106	60	60	60	61	62	63	64
	90th	111	112	113	114	116	118	120	74	74	74	74	74	75	75
	95th	115	116	117	118	120	123	124	76	77	77	77	77	77	77
	95th +12 mmHg	127	128	129	130	132	135	136	88	89	89	89	89	89	89
12	Height-inches	56.2	57.3	59	60.9	62.8	64.5	65.5	56.2	57.3	59	60.9	62.8	64.5	65.5
	Height-cm	142.8	145.5	149.9	154.8	159.6	163.8	166.4	142.8	145.5	149.9	154.8	159.6	163.8	166.4
	50th	102	102	104	105	107	108	108	61	61	61	62	64	65	65
	90th	114	115	116	118	120	122	122	75	75	75	75	76	76	76
	95th	118	119	120	122	124	125	126	78	78	78	78	79	79	79
	95th +12 mmHg	130	131	132	134	136	137	138	90	90	90	90	91	91	91

(continued)

**Table 2** (continued)

13	Height-inches	58.3	59.3	60.9	62.7	64.5	66.1	67	58.3	59.3	60.9	62.7	64.5	66.1	67
	Height-cm	148.1	150.6	154.7	159.2	163.7	167.8	170.2	148.1	150.6	154.7	159.2	163.7	167.8	170.2
	50th	104	105	106	107	108	108	109	62	62	63	64	65	65	66
	90th	116	117	119	121	122	123	123	75	75	75	76	76	76	76
	95th	121	122	123	124	126	126	127	79	79	79	79	80	80	81
	95th +12 mmHg	133	134	135	136	138	138	139	91	91	91	91	92	92	93
14	Height-inches	59.3	60.2	61.8	63.5	65.2	66.8	67.7	59.3	60.2	61.8	63.5	65.2	66.8	67.7
	Height-cm	150.6	153	156.9	161.3	165.7	169.7	172.1	150.6	153	156.9	161.3	165.7	169.7	172.1
	50th	105	106	107	108	109	109	109	63	63	64	65	66	66	66
	90th	118	118	120	122	123	123	123	76	76	76	76	77	77	77
	95th	123	123	124	125	126	127	127	80	80	80	80	81	81	82
	95th +12 mmHg	135	135	136	137	138	139	139	92	92	92	92	93	93	94
15	Height-inches	59.7	60.6	62.2	63.9	65.6	67.2	68.1	59.7	60.6	62.2	63.9	65.6	67.2	68.1
	Height-cm	151.7	154	157.9	162.3	166.7	170.6	173	151.7	154	157.9	162.3	166.7	170.6	173
	50th	105	106	107	108	109	109	109	64	64	64	65	66	67	67
	90th	118	119	121	122	123	123	124	76	76	76	77	77	78	78
	95th	124	124	125	126	127	127	128	80	80	80	81	82	82	82
	95th +12 mmHg	136	136	137	138	139	139	140	92	92	92	93	94	94	94
16	Height-inches	59.9	60.8	62.4	64.1	65.8	67.3	68.3	59.9	60.8	62.4	64.1	65.8	67.3	68.3
	Height-cm	152.1	154.5	158.4	162.8	167.1	171.1	173.4	152.1	154.5	158.4	162.8	167.1	171.1	173.4
	50th	106	107	108	109	109	110	110	64	64	65	66	66	67	67
	90th	119	120	122	123	124	124	124	76	76	76	77	78	78	78
	95th	124	125	125	127	127	128	128	80	80	80	81	82	82	82
	95th +12 mmHg	136	137	137	139	139	140	140	92	92	92	93	94	94	94
17	Height-inches	60.0	60.9	62.5	64.2	65.9	67.4	68.4	60.0	60.9	62.5	64.2	65.9	67.4	68.4
	Height-cm	152.4	154.7	158.7	163.0	167.4	171.3	173.7	152.4	154.7	158.7	163.0	167.4	171.3	173.7
	50th	107	108	109	110	110	110	111	64	64	65	66	66	66	67
	90th	120	121	123	124	124	125	125	76	76	77	77	78	78	78
	95th	125	125	126	127	128	128	128	80	80	80	81	82	82	82
	95th +12 mmHg	137	137	138	139	140	140	140	92	92	92	93	94	94	94

Use percentile values to stage BP readings according to the scheme in Table 1: Elevated BP:  $\geq 90$ th percentile; stage 1 HTN:  $\geq 95$ th percentile; stage 2 HTN:  $\geq 95$ th percentile +12 mmHg. The 50th, 90th, and 95th percentiles were derived using quantile regression based on normal weight children (BMI percentile  $< 85$ ) (Rosner et al. 2008)

### Routine Blood Pressure Screening, Diagnosis of Hypertension, and Use of Ambulatory Blood Pressure Monitoring

While the prior NHBPEP guidelines recommended routine measurement of BP in children and adolescents for screening purposes at every health care

encounter, the 2017 AAP CPG recommends that routine BP screening be carried out only at annual preventive care visits, unless the patient has a predisposing condition associated with HTN such as obesity, diabetes, heart disease, or kidney disease. Such a recommendation acknowledges the controversy regarding routine screening of BP in childhood to some extent (Semaniak and Flynn 2016), but still supports limited screening as a potential



**Table 3** Screening blood pressure values requiring further evaluation

Age, years	Blood pressure, mmHg			
	Boys		Girls	
	Systolic	Diastolic	Systolic	Diastolic
1	98	52	98	54
2	100	55	101	58
3	101	58	102	60
4	102	60	103	62
5	103	63	104	64
6	105	66	105	67
7	106	68	106	68
8	107	69	107	69
9	107	70	108	71
10	108	72	109	72
11	110	74	111	74
12	113	75	114	75
≥13	120	80	120	80

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way to uncover cases of secondary HTN. Diagnosis of HTN is still based upon demonstration of elevated or hypertensive-level BP at three encounters unless the patient is symptomatic, with auscultation as the preferred method of BP measurement. The CPG also includes detailed recommendations for the correct technique of office BP measurement, along with a link to an AAP-produced video illustrating the procedure.

Ambulatory blood pressure monitoring (ABPM) is recommended in several places within the 2017 AAP CPG, including the following:

- Confirmation of the diagnosis of HTN in children and adolescents with repeatedly elevated office BP readings (moderate recommendation, level C evidence)
- Confirmation of suspected white coat HTN (strong recommendation, level B evidence)
- Evaluation for masked HTN in children and adolescents with a history of repaired coarctation of the aorta (strong recommendation, level B evidence)
- Evaluation of BP pattern and risk for hypertensive target organ damage (TOD) in children and adolescents with high-risk conditions such as chronic kidney disease (CKD; moderate recommendation, level B evidence)

- Evaluation for possible HTN in children and adolescents with obstructive sleep apnea syndrome (weak recommendation, level D evidence)
- Evaluation of BP in pediatric heart and kidney transplant recipients (weak recommendation, level D evidence)
- Assessment of treatment effectiveness in children and adolescents receiving antihypertensive medications (moderate recommendation, level B evidence)
- Monitoring of treatment efficacy and possible masked HTN in children and adolescents with CKD (strong recommendation, level B evidence)

A standardized approach to the performance of ABPM is recommended, essentially the same approach that is outlined in the 2014 AHA Scientific Statement on pediatric ABPM (Flynn et al. 2014). Finally, routine performance of ABPM to confirm HTN is also endorsed from a cost-effectiveness standpoint, given the high prevalence of white coat HTN in children. That endorsement is predicated on the assumption that patients found to have WCH would not need to undergo further diagnostic workup such as extensive laboratory testing and/or imaging.

The focus on ABPM is consistent with other recent consensus recommendations for its use in adults, including the NICE guideline (National Institute for Health and Care Excellence 2011) and the most recent recommendations from the United States Preventative Services Task Force (Siu and U.S. Preventive Services Task Force 2015). However, while both of these adult guidelines state that home BP monitoring (HBPM) could be used as an alternative to ABPM if ABPM were unavailable, the AAP Subcommittee found insufficient evidence to support the use of HBPM for the diagnosis of HTN in children and adolescents. The recommendation not to use HBPM for diagnosis may lead to problems with full implementation of the ABPM recommendations in the 2017 AAP CPG, as many primary care providers may not have ready access to pediatric ABPM without referring their patients to subspecialists such as

pediatric nephrologists or pediatric cardiologists. Hopefully, pediatric ABPM will become more widely available as a result of the publication of these updated recommendations. However, until that time, reliance on office BP measurements and/or subspecialty referral may need to be substituted when ABPM is not immediately available.

### **Hypertensive Target-Organ Damage: Left Ventricular Hypertrophy**

It has long been recognized from cross-sectional studies that hypertensive children and adolescents are at risk of development of hypertensive TOD; left ventricular hypertrophy (LVH) has been the most commonly studied form of TOD in children and adolescents, as it is readily assessed by echocardiography. The 2004 Fourth Report (NHBEP Working Group 2004) recommended routine performance of echocardiography to assess for possible LVH at the time of diagnosis of HTN and adopted an indexed left ventricular mass (LVM) of  $51.7 \text{ gm/m}^2$  as the cut-point for diagnosing LVH. Since publication of the Fourth Report, however, several new approaches to diagnosing and defining LVH in children and adolescents have been published, leading to uncertainty as to the correct definition of pediatric LVH (Sethna and Leisman 2016).

Given that uncertainty, the AAP Subcommittee convened a special panel of pediatric cardiologists to perform a detailed examination of the literature on pediatric LVH, with an emphasis on establishing a consensus LVM cut-point for diagnosis of LVH, as well as examination of when echocardiography should be performed. The resulting recommendations have important differences from the recommendations that appeared in the 2004 Fourth Report:

- *Definition of LVH:* Similar to the 2004 Fourth Report, the panel recommended that a left ventricular (LV) mass  $> 51 \text{ gm/m}^2$  should be used to define LVH for children and adolescents greater than 8 years of age, but that LVH could also be defined as LV mass  $> 115 \text{ g/BSA}$  for boys and LV mass  $> 95 \text{ g/BSA}$  for girls. Additionally, the

panel recognized that additional study is needed to better understand the clinical significance of LV mass between the 95th percentile according to published normative data (Khoury et al. 2009) and the  $51 \text{ gm/m}^2$  LVH cut-point.

- *Other forms of cardiac TOD:* Both concentric LVH and decreased LV ejection fraction are defined and discussed in the new CPG; these were not explicitly defined in the 2004 Fourth Report.
- *Timing of echocardiography:* Whereas the 2004 Fourth Report recommended that echocardiograms be obtained in all hypertensive children and adolescents at the time of diagnosis of HTN, it is now recommended that echocardiograms be obtained to assess for cardiac TOD at the time when pharmacologic treatment for HTN is being considered. Additional time points for consideration of echocardiography include monitoring of known TOD, or when HTN persists despite treatment, and when concentric LVH or reduced LV ejection fraction is present on the initial echocardiogram. Finally, the CPG suggests that repeat echocardiography could be considered when patients do not have TOD at time of initial echocardiographic assessment, or in patients with stage 2 HTN, secondary HTN, or incompletely treated stage 1 HTN. In these patients, the purpose of repeat echocardiography would be to assess for development or worsening of TOD.

The 2017 AAP CPG also addresses testing for other forms of hypertensive TOD that are becoming used more widely in adult cardiovascular medicine, including testing for microalbuminuria, assessment of carotid intimal-medial thickness, and assessment of pulse wave velocity. While there is recognition that such studies are useful from a research standpoint in hypertensive children and adolescents, routine clinical use is not endorsed at this time.

### **Antihypertensive Drug Therapy and Its Goals**

Indications for use of antihypertensive medications in children and adolescents with HTN have always been opinion-based, given lack of evidence that such treatment will prevent future

cardiovascular events, the major rationale for such treatment in adults. The lack of extensive pediatric efficacy and safety information for many antihypertensive medications in the past has also been influential, as there has been reluctance to expose pediatric patients to medications of unknown safety and efficacy in the absence of a clear benefit. Recommendations for drug treatment in the 2004 Fourth Report were, therefore, mostly limited to patients with secondary forms of HTN, those with hypertensive TOD, and those with more severe HTN, with one additional recommendation that drug treatment be considered for patients with persistent HTN, despite lifestyle changes (NHBEP Working Group 2004).

A similarly limited set of indications for antihypertensive medications is found in the 2017 AAP CPG:

- Persistent HTN despite lifestyle modification, especially with an abnormal echocardiogram
- Symptomatic HTN
- Stage 2 HTN without a modifiable risk factor
- Any stage of HTN in patients with diabetes mellitus (DM) or chronic kidney disease (CKD)

The major difference in 2017 compared to 2004 is that nearly all of the newer antihypertensive medications have been studied in children as a result of legislative initiatives in the United States and Europe (see ► [Chapter 38, “Changes in Drug Development Regulations and Their Impact on Clinical Trials”](#)), so there is now a wider variety of agents with pediatric efficacy and safety data available from which to select when drug therapy is indicated. Angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), long-acting calcium channel blockers, or thiazide diuretics are the recommended initial agents for patients with primary HTN, and a strong recommendation is made for use of an ACEI or ARB as the initial agent in hypertensive patients with CKD, DM, or proteinuria. As in the 2004 Fourth Report, an updated list of recommended drug doses is provided.

BP treatment targets in the 2017 AAP CPG are straightforward: goal BP is <90th percentile for

age or <130/80 mmHg, whichever is lower (based upon office/casual BP readings). These targets are based on new data published since the 2004 Fourth Report that have shown that hypertensive TOD can appear at BP levels between the 90th and 95th percentiles, and that BP reduction below the 90th percentile can reverse LVH. Recommendations for hypertensive children and adolescents with CKD, however, are different: BP should be monitored by ABPM, and the recommended goal BP is a 24-h mean arterial pressure (MAP) <50th percentile. This recommendation is based upon compelling data from the ESCAPE trial that demonstrated a slower rate of progression of CKD in patients treated to 24-h MAP <50th percentile compared to those treated to a 24-h MAP of <90th percentile (Wühl et al. 2009).

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## Conclusions

The 2017 AAP CPG is a comprehensive document that addresses numerous aspects of the evaluation and management of high BP in children and adolescents. It is the first pediatric HTN guideline to be developed from a strict evidence-based approach as recommended by the NHLBI (Gibbons et al. 2013) and the first to be aligned as much as possible with a new HTN guideline for adults. While many of its recommendations are similar to those found in the 2004 Fourth Report, the many studies on childhood HTN that have been published since 2004 have provided important data that has led to notable modifications of the 2004 recommendations and generation of entirely new ones. It is expected that as additional studies are conducted in the years to come, further updates will reflect the new evidence and will provide additional guidance to practitioners who evaluate children and adolescents with high BP.

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## Cross-References

- [Changes in Drug Development Regulations and Their Impact on Clinical Trials](#)
- [Development of Blood Pressure Norms and Definition of Hypertension in Children](#)

- ▶ Pharmacologic Treatment of Pediatric Hypertension
- ▶ Sequelae of Hypertension in Children and Adolescents
- ▶ Value of Routine Screening for Hypertension in Childhood

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