Clinical Hypertension and Vascular Diseases
Series Editor: William B. White

Joseph T. Flynn
Julie R. Ingelfinger
Ronald J. Portman *Editors*

Pediatric Hypertension

Third Edition

Humana Press

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Foreword

Hypertension in children and adolescents has become more commonplace, and it is a disease that directly causes target organ damage, is associated with premature vascular disease and places the affected child at greater risk for hypertension and its complications as an adult. The third edition of *Pediatric Hypertension*, is *the* reference textbook for clinicians and investigators who are involved with evaluation and management of childhood hypertension. The new edition follows the second edition by only 2–3 years but is clearly updated from the prior edition of the book published in 2011 – there are several new chapters, and some previous chapters have been modified and have new authors. Thus, this third edition of *Pediatric Hypertension* is a comprehensive textbook of 38 chapters that remain divided into four broad themes: I. Regulation of blood pressure and pathophysiologic mechanisms of hypertension; II. Assessment of blood pressure in children including measurement, normative data, and epidemiology; III. Hypertension in Children that includes predictors, risk factors and special populations; and IV. Evaluation and treatment of pediatric hypertension.

As in the prior editions of this book, the chapters are written by experts in their respective fields and remain well-written and organized in a clear and logical fashion. The first section has been re-organized and now includes chapters on perinatal programming and experimental models in childhood hypertension. The chapter on cardiovascular influences has been rewritten. The second section of the book has new chapters on ambulatory blood pressure monitoring in children as well as cardiovascular risk assessment in children and adolescents. The third section has been expanded substantially to encompass more in-depth discussion of stress and salt sensitivity and also important clinical sub-populations with vascular and endocrine hypertension as well as management of the pregnant teenager with hypertension. In this third edition, there are also discrete new chapters on cognitive and behavioral aspects of childhood hypertension as well as regulatory aspects of drug development for children and adolescents. The material in each chapter is presented in a lucid manner, with clearly interpreted results and extensive referencing. Clinical applications are given so that the clinician can better incorporate this material into their understanding of the pathophysiology of hypertension in neonates, children, and adolescents.

The chapters in *Pediatric Hypertension* will be helpful for trainees in pediatrics and its sub-specialties as well as practicing clinicians due to their

pragmatic nature. The updated chapters as well as new materials noted above make the book the most comprehensive and up-to-date reference in the field of hypertension and its complications in children.

As series editor of *Clinical Hypertension and Vascular Diseases*, I am both enthusiastic and proud of the extremely high quality of the third edition of *Pediatric Hypertension.* In addition, the editors have a good deal to be proud about as well as they have persisted in bringing this third edition of their book to the public in record time and by doing so have a very contemporary textbook for their audience. I am certain that pediatricians, primary care providers and all physicians with an interest in clinical and translational aspects of hypertension and its complications will find *Pediatric Hypertension* an important and worthwhile addition to their library.

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Preface

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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Part I

Regulation of Blood Pressure and Pathophysiological Mechanisms of Hypertension

Neurohumoral and Autonomic Regulation of Blood Pressure

1

Jeffrey L. Segar

Abstract

Neural, hormonal, and metabolic mechanisms are involved in setting blood pressure. These components act both systemically and locally. 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 adult humans and experimental models. This chapter focuses on the role of these mechanisms during fetal and postnatal development. 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 will consider autonomic control of the fetal and postnatal cardiovascular system and will discuss humoral factors that act within the central nervous system to influence sympathovagal balance.

Keywords

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

Introduction

Cardiovascular homeostasis is mediated through interacting neural, hormonal, and metabolic mechanisms that act both locally and systemically. These basic physiological mechanisms, which have been extensively studied in the adult, are functional earlier, during development, although differential rates of maturation of these systems influence their ability to maintain blood pressure and delivery of oxygen and nutrients. This chapter focuses on autonomic control of the fetal and postnatal cardiovascular system and how humoral factors acting within the central nervous system influence sympathovagal balance.

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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 the contractile force of the heart (see Chaps. 1, 2, and 3). Thus, blood pressure is maintained through 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 input 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 [1]. 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) [2]. Second-order neurons originating from the NTS project to and excite, via glutamatergic synapses, the caudal and rostral ventrolateral medulla (VLM). Sympathoexcitatory neurons in the rostral VLM project via the intermediolateral cell column of the spinal cord to cardiac and vasomotor sympathetic ganglia. Baroreceptor signals are also transmitted to supramedullary regions. An important aspect of this reflex loop is the ability of circulating signaling molecules, such as angiotensin II (ANG II), to act on autonomic control centers in the hypothalamus and medulla to regulate efferent neural outputs. Although these centers are protected behind the blood-brain barrier, a group of specialized central nervous systems structures, the circumventricular organs, which lack a blood-brain barrier, are able to sense these peripheral signals and transmit information via neural projections to these hypothalamic autonomic control centers (reviewed in Smith [3]). Specialized anatomic features such as dense fenestrated capillaries and receptors for peripheral signals allow circumventricular organs to directly monitor elements in the peripheral circulation and communicate this information directly to cardiovascular centers in the medulla and hypothalamus.

Tonic Autonomic Activity

The contribution of the tonic baseline level of autonomic activity to the maintenance of blood pressure is difficult to assess directly and likely changes during development. The hypotensive response to ganglionic blockade may be used an as index of the neurally mediated contribution to blood pressure. Both α (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 [4, 5]. The influence of the parasympathetic system on resting heart rate also appears to increase with maturation [6]. 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 [5, 7, 8]. In rats, the sympathetic nervous system appears much more immature at birth as ganglionic blockade in the first 24–36 h of life has no effect on resting blood pressure [9]. At an early age, ganglionic transmission appears to be the rate-limiting step in efferent sympathetic control, and 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, an adrenergic compensatory response.

Direct recordings of muscle sympathetic nerve activity (MSNA) in humans indicate that baseline nerve activity varies widely in normotensive adults, with little relations between MSNA and blood pressure under 40 years of age [10]. With aging, modest increases in both MSNA and blood pressure occur, with MSNA about twofold greater in healthy 60–70-year-olds compared to younger adults [11, 12]. Ganglionic blockade produces a greater decrease in blood pressure in older compared to young adults, consistent with greater sympathetic support of blood pressure in older subjects [13]. Interestingly, there appears to be an inverse relationship between plasma nitrates (a marker of whole-body nitric oxide production) and MSNA, suggesting that a high vasodilator tone might limit blood pressure effects of high sympathetic traffic [10].

Arterial pressure displays natural oscillations within a physiological range, similar in fetal and postnatal life [14–17]. 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 [14, 18]. In contrast, ganglionic blockade in term fetal sheep significantly attenuates heart rate and arterial pressure variability [16]. Booth et al. identified entrainment or rhythmicity of RSNA 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 [19]. 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 [19–24]. 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 [20, 25, 26].

Arterial Baroreflex

Arterial baroreceptors, the major sensing elements of the cardiovascular regulatory system, are essential in short-term control of blood 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 [27, 28]. 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 [29]. Animal studies demonstrate that the arterial baroreflex is functional during fetal and early postnatal life [6, 17, 30–32]. 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 [17, 31].

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 [33–37]. The sensitivity of carotid baroreceptors to increases in carotid sinus pressure is greater in fetal than in newborn and 1-month-old lambs [34] and in newborn compared to adult rabbits [37]. 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 [38–43].

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 [44–48]. 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 [32]. 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 [49].

Developmental changes in the cardiac baroreflex continue postnatally. Heart rate responses to pharmacologically induced increases and decreases in blood pressure in fetal (135 ± 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 [50]. Other studies in sheep [47] and other species [51, 52] 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 [51]. Age-related changes in heart rate in response to phenylephrine are also greater in 2-month-old piglets than in 1-day-old animals [52]. 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.

Baroreflex control of central sympathetic outflow, primarily measured as renal sympathetic nerve activity (RSNA), has also been assessed. Booth et al. demonstrated in the preterm fetal sheep (0.7 of gestation) that baroreflex control RSNA was absent although pulse-synchronous bursts of RSNA were present [32]. 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 [53]. 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 (135 ± 2-day gestation), 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 [50]. Interestingly, studies in aging animals have shown that baroreflex control of heart rate and sympathetic nerve activity is impaired with senescence [54]. 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 [39, 40] and sensitivity for resetting changes with maturation. With sustained changes in blood pressure, the operating range of the baroreceptors also 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 occurs during fetal life, is present immediately after birth, and continues with postnatal maturation, paralleling the naturally occurring increase in blood pressure [55]. The mechanisms regulating developmental changes in baroreflex sensitivity and controlling the resetting of the baroreflex are poorly understood. Changes in the relationship between arterial pressure and sympathetic activity or heart rate occur at the level of the baroreceptor itself (peripheral resetting), 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 [39]. Locally produced factors, such as nitric oxide,

and circulating hormones and neuropeptides, such as ANG II and vasopressin (AVP), activate additional neural reflex pathways that may modulate the changes in arterial baroreflex during development [56].

Autonomic Function During Human Development

In the human infant, neural control of the circulation may be assessed by analysis of heart rate indices at rest and in response to postural changes. While some investigators have been unable to demonstrate a consistent response of heart rate to tilting and concluded that the heart rate component of the baroreflex is poorly developed during the neonatal period, others have demonstrated in healthy preterm and term infants that unloading arterial baroreceptor by head-up tilting produces a significant heart rate response [57–59]. Using venous occlusion plethysmography, Waldman et al. [59] 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 [60]. However, at 2–4 months of age, the increase in heart rate to unloading of baroreceptors (head-up tilt) is lost [60, 61].

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 [62–64] and fetuses [65–67] 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 [65]. 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. Clairembault 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 [64]. 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 weeks post-conceptional age [68]. Longitudinal examination of heart rate power [68] 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. 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 [62]. 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 [69]. 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 [70]. 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. [71] found that spontaneous baroreflex sensitivity was decreased in prone

compared to supine infants at 2–3 and 5–6 months of age while baroreflex sensitivity increased with postnatal age. A study of blood pressure and heart rate variability in this same population found blood pressure LF/HF ratio decreases with postnatal age, suggesting a withdrawal or decrease in sympathetic vascular modulation over this period while parasympathetic control of heart rate strengthened.

In adults, initial stages of hypertension are associated with elevated sympathetic drive and baroreflex impairment. Studies of the contribution of these factors in children are limited. 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 [72]. These data suggest that early autonomic dysfunction, including baroreflex impairment, could contribute to the later development of hypertension in a subset of children.

Cardiopulmonary Reflex

Cardiopulmonary receptors are sensory endings located in the four cardiac chambers, in the great veins, and in the lungs [73]. In the adult, volume sensors mediating reflex changes in cardiovascular and renal function are believed to be primarily those residing in the atria [74, 75] and the ventricles [73], with the ventricular receptors being of utmost importance during decreases in cardiopulmonary pressures [73, 76, 77]. 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) [78, 79]. These receptors have a low basal discharge rate which exerts a tonic inhibitory influence on sympathetic outflow and vascular resistance[73] and regulates plasma AVP concentration [80]. 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 [73].

Characterization of the cardiopulmonary reflex during the perinatal and neonatal periods was initially performed by stimulation of chemosensitive cardiopulmonary receptors [52, 81, 82]. 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 [83, 84]. 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 [85]. 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.

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 days gestation, whereas blood pressure remains stable and heart rate increased in near-term fetuses [86]. However, other investigators [87, 88] 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 [87]. 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 [89], whereas vagotomy with SAD enhances the decrease in blood pressure [87]. 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 [90]. In addition, the cardiovascular responses to hemorrhage in newborn lambs are dependent upon intact renal nerves that in turn modulate release of AVP [91].

The RSNA responses to vagal afferent nerve stimulation are similar in sinoaortic-denervated fetal and postnatal lambs [92], suggesting that delayed maturation of the cardiopulmonary reflex is not secondary to incomplete central integration of vagal afferent input. 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 [93, 94] suggest that activation of arterial baroreceptors may impair the reflex responses to activation of cardiopulmonary receptors.

Peripheral Chemoreflex

Peripheral chemoreceptors located in the aortic arch and carotid bodies are functional during fetal and postnatal life and participate in cardiovascular regulation [95–97]. 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 [96, 98]. Oxygen sensing in the carotid body is transduced by glomus cells, specialized sensory neurons that respond to hypoxia at higher PaO_2 levels than other cell types. It is believed that in states of low O_2, oxygen-sensitive K^+ currents are inhibited, resulting in depolarization, an influx of Ca^{2+}, and the release of neurotransmitters and neuromodulators which generate an action potential in the carotid sinus nerve [99]. The bradycardia associated with hypoxemia is mediated by parasympathetic efferents, while the initial vasoconstriction results from increased sympathetic tone [97, 100]. The release of circulating factors such as AVP and catecholamines serves to maintain peripheral vasoconstriction while heart rate returns toward basal levels.

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 [97, 101–104]. The cardiovascular response to acute fetal hypoxemia depends upon the prevailing intrauterine condition, including the redox state of the fetus [98, 105–110]. In fetal sheep, mild, acute acidemia (pH 7.29 ± 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 [107]. To examine the effects of prevailing hypoxemia on responses to acute hypoxemia, Gardner et al. [98] studied chronically instrumented fetal sheep grouped according to PaO_2. Functional chemoreflex analysis during early hypoxemia, performed by plotting the change in 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 [106]. 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 [111]. 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 PaO_2 relative to control animals [112]. 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 [113, 114]. 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 [114, 115]. The mechanisms involved with this resetting are not known, although the postnatal rise in PaO_2 appears crucial as raising fetal PaO_2 produces a rightward shift in the response curve of carotid baroreceptors to differing oxygen tension [116]. Potential mechanisms within the glomus cell regulating developmental changes in O_2 transduction and chemoreceptor responses include, but are not limited to, anatomical maturation, developmental changes in oxygen-sensitive K^+ currents, adenosine responsiveness [117, 118], dopamine and catecholamine turnover within the carotid body [119], and differences in intracellular calcium mobilization during hypoxia [99, 120].

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 [121, 122]. Activation of the sympathetic nervous system appears to be an important part of this adaptive process and is associated with marked increases in circulating catecholamine [123, 124]. 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 [125]. 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 [55]. Delivery appears to produce near maximal stimulation of renal sympathetic outflow since further increases cannot be elicited by unloading of arterial baroreceptors [55]. 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 [50], 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 reflex inhibition has been well described in adult animals as part of the defense reaction [126].

The factors mediating the increase in sympathetic outflow at birth are unclear. 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 [127, 128]. 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 [129], suggesting that lung inflation and an increase in arterial oxygen tension contribute little to the sympathoexcitation process. The increases in heart rate, mean arterial blood pressure, and RSNA following delivery are similar in intact and sinoaortic-denervated plus vagotomized fetal lambs [130], demonstrating that afferent input from peripheral chemoreceptors and mechanoreceptors also contribute little to the hemodynamic and sympathetic responses at delivery.

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 [131, 132]. Fetal cooling, but not ventilation or umbilical cord occlusion, initiates nonshivering thermogenesis via neurally mediated sympathetic stimulation of brown adipose tissue [133]. In utero cooling of fetal lambs also produces an increase in RSNA of similar magnitude to that seen at delivery by cesarean section [59], 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.

Neuroanatomical studies have shown that nuclei within the hypothalamus project directly to a number of areas in the hindbrain containing preganglionic sympathetic and parasympathetic neurons, including the rostral and caudal ventrolateral medulla, the intermediolateral cell column, and the dorsal motor nucleus of the vagus [134–136]. In fetal sheep, electrical stimulation of the hypothalamus evokes tachycardia and a pressor response which are attenuated by α(alpha)-adrenoreceptor blockade [137]. Stimulation of the dorsolateral medulla and lateral hypothalamus in the newborn piglet similarly increases blood pressure and femoral blood flow [52]. Since the responses to hypothalamic stimulation are lost during stress (hypoxia, hypercapnia, hemorrhage) while those elicited from the medulla are not, some investigators have proposed that the hypothalamus exerts little influence of cardiovascular function until later in postnatal development [52]. However, other studies suggest forebrain structures are vital for normal physiological adaptation following the transition from fetal to newborn life. The increases in heart rate, mean arterial blood pressure, and RSNA which 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 [129]. Ablation of the paraventricular nucleus of the hypothalamus in fetal sheep also attenuates the postnatal increase in sympathetic outflow and alters baroreflex function [138]. Thus, supramedullary structures appear intimately involved in the regulation of circulatory and autonomic functions during the transition from fetal to newborn life.

The hemodynamic and sympathetic responses at birth are markedly different in prematurely delivered lambs (0.85 of gestation) compared to those delivered at term [139]. Postnatal increases in heart rate and blood pressure are attenuated, and the sympathoexcitatory response as measured by RSNA is absent [139]. 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 [139]. 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 [139]. The mechanisms are unclear, though stimulation of the peripheral RAAS and activation of peripheral angiotensin receptors are not involved [140].

Humoral Factors (See Also Chaps. 1 and 2)

Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system (RAAS) is active in the fetal and perinatal periods [141–143]. 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 [144]. Only later during fetal development does the renin-angiotensin system become involved in modulating cardiovascular function and renal hemodynamics. Many studies report that administration of inhibitors of the RAAS, including angiotensin-converting enzyme inhibitors and ANG II subtype 1 receptor blockers, decreases fetal and newborn arterial blood pressure [142, 145–147]. Plasma renin activity is elevated during the newborn period, declines rapidly in the first year of life, and then gradually declines further until adulthood [148, 149]. In preterm infants, plasma renin activity is markedly elevated and has close inverse relationship to postconceptual age [150].

Fetal plasma renin activity and plasma ANG II concentration increase after aortic constriction, hypotension, and blood volume reduction [141]. Conversely, increases in arterial blood pressure and volume expansion reduce plasma renin activity in fetal and newborn animals [151].

The vasopressor response and renal vascular reactivity to exogenous ANG II are less in fetal lambs than in adult sheep [152]. One may speculate that differences in the localization and expression of the ANG II receptor subtypes contribute to this effect.

While baroreceptors and chemoreceptors regulate the release of vasoactive hormones, such as ANG II [56, 153], changes in the levels of these circulating hormones, in turn, influence neural regulation of cardiovascular function. For example, in the sheep fetus, the increase in arterial blood pressure produced by ANG II administration produces little or no cardiac slowing [152, 154], although dose-dependent decreases in heart rate may occur [155, 156]. The bradycardic and sympathoinhibitory responses to a given increase in blood pressure are less for ANG II than for other vasoconstrictor agents [157]. In the adult ANG II facilitates activation of sympathetic ganglia and enhances the release of norepinephrine at the neuroeffector junction [158].

Within the central nervous system, ANG II stimulates sympathetic outflow and alters baroreceptor reflexes by acting on ANG II type 1 (AT_1) receptors located within the hypothalamus, medulla, and circumventricular organs [159–161]. In the sheep fetus, endogenous brain ANG II appears to contribute little to basal arterial pressure. However, lateral ventricle injection of ANG II increases blood pressure, an effect blocked by AT_1 receptor antagonists [162–164]. 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_1 receptor abundant [162–164]. Lateral ventricle administration of an AT_1 but not AT_2 receptor antagonist also 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 [165]. 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 [166].

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 [145] as well in human adults and infants [63]. In the newborn lamb, angiotensin-converting enzyme inhibition or AT_1 receptor blockade decreases RSNA and heart rate and resets the baroreflex toward lower pressure [157, 165]. 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 [153, 167–169]. 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 [170, 171]. AVP infusion increases fetal blood pressure and decreases fetal heart rate in a dose-dependent manner [172, 173], 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 [174, 175]. However, AVP receptor inhibition impairs the ability of the fetus to maintain blood pressure during hypotensive hemorrhage and reduces the catecholamine response [176].

In several adult species, AVP modulates parasympathetic and sympathetic tone and baroreflex function [56, 175, 177, 178]. Administration of AVP evokes a greater sympathoinhibition and bradycardia than other vasoconstrictors for a comparable increase in blood pressure [56, 178], attributed to AVP enhancing the gain of the reflex and resetting it to a lower pressure [56, 178].

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 [175].

Endogenous AVP has little effect on baroreflex function early during development. Peripheral administration of a V_1-receptor antagonist has no measurable effects on resting hemodynamics in fetal sheep or on basal arterial blood pressure [174], heart rate, RSNA, or baroreflex response in newborn lambs [175]. 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 [179]. 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 [180]. The changes in blood pressure and heart rate are completely inhibited by administration of an AVP receptor type 1 (V_1) antagonist, demonstrating that central cardiovascular effects of AVP are mediated by V_1 receptors, as has been reported in mature animals [181].

Glucocorticoids

The prepartum 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 [182, 183]. Antenatal exposure to exogenous glucocorticoids increases fetal and postnatal arterial blood pressure by enhancing peripheral vascular resistance and cardiac output without altering heart rate [184–186]. The use and effectiveness of hydrocortisone for hypotension in preterm and term neonates is well described [187, 188]. 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 [189, 190]. In contrast, glucocorticoids enhance pressor responsiveness and vascular reactivity to norepinephrine and angiotensin II [191, 192], in part by increasing α_1-adrenergic and AT_1 receptor levels and potentiating angiotensin II and vasopressin-induced inositol triphosphate production [193, 194]. Glucocorticoids also reduce the activity of depressor systems, including vasodilator prostaglandins and nitric oxide, and have been shown to decrease serum $NO2^-/NO3^-$, endothelial nitric oxide synthase mRNA stability and protein levels [195].

In the sheep fetus, cortisol infusion increases blood pressure as well as the hypertensive response to intravenous ANG II but not norepinephrine [182]. However, infusions of synthetic glucocorticoids, which also increase arterial blood pressure, do not alter the pressor response to phenylephrine, angiotensin II, or vasopressin [196]. Furthermore, the increase in blood pressure is not inhibited by RAAS blockade [140]. 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 [197]. 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 [197–200].

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 [139, 184, 201]. Circulating neuropeptide Y concentration, which may provide an index of peripheral sympathetic activity,

is increased following fetal exposure to dexamethasone [202]. Glucocorticoid treatment accelerates postnatal maturation of brain catecholaminergic signaling pathways in rats and enhances renal sympathetic nerve activity in prematurely delivered lambs [84, 203, 204].

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 [205]. 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 [205]. Antenatal administration of betamethasone decreases the sensitivity of baroreflex-mediated changes in heart rate in preterm fetuses and premature lambs [139] and alters baroreflex and chemoreflex function in fetal, newborn, and adult sheep [196, 201, 206, 207]. 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 [208]. Sympathetic-mediated responses to behavioral or pharmacological challenges are also exaggerated in 6-week-old sheep following antenatal betamethasone exposure [206]. Glucocorticoid exposure also appears to alter chemoreflex-mediated cardiovascular responses. In response to acute hypoxia, fetuses exposed to exogenous corticosteroids display prolonged bradycardia and attenuated plasma catecholamine and vasopressin responses [202]. In all, it appears that glucocorticoids modify autonomic and endocrine control of cardiovascular function during development. However, in humans, exposure to antenatal glucocorticoids has not been associated with increased blood pressure in childhood, and indicators of cardiac autonomic balance including heart rate variability and sympathovagal balance are preserved [209, 210]. Studies of humans long after glucocorticoid administration are necessary to determine if persistent effects on autonomic and cardiovascular function exist.

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 [211, 212], which suggests that NO may function as a neurotransmitter to regulate arterial blood pressure in addition to its local regulation of vascular tone [213–215]. In adult rats, NO within the paraventricular nucleus may exert a sympathoinhibitory effect [216]. Downregulation of neuronal NO synthase in the NTS reduces baroreflex tachycardic responses to acute hypotension but not reflex bradycardia to acutely increased blood pressure [217]. 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 [218]. 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 4th ventricle increases fetal blood pressure [219]. Expression of NO synthase isoforms in the fetal sheep brain stem is highest early in gestation and decreases with advancing age [220]. 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 [221]. 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 [221].

Reactive Oxygen Species

Reactive oxygen species signaling has emerged as a major signaling mechanism of sympathetic activation. For example, increased reactive oxygen species production in the rostral ventrolateral medulla enhances central sympathetic outflow, leading to hypertension [222]. Oxidative stress appears to be a key mechanism in ANG II-dependent neurogenic hypertension [223]. 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 [224]. In juvenile rats (19–21 day of age), chronic intermittent hypoxia for 10 days results in significantly increased blood pressure and sympathetic overactivity, though cardiac baroreflex function remains intact [225, 226]. 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 [108–110]. Whether these effects are mediated through mechanism similar to those described in the adult is not known.

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, and their interactions, during relevant pathophysiological conditions.

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Vasoactive Factors and Blood Pressure in Children

2

Ihor V. Yosypiv

Abstract

Control of arterial blood pressure (BP) is accomplished by the net effect of vasodilator and vasoconstrictor substances. This chapter presents updated data on the ontogeny of the most relevant vasoactive 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.

Keywords

Vasoactive peptides • Renin–angiotensin • Prorenin receptor • Nitric oxide

Introduction

Vasoactive peptide systems play a critical role in the regulation of arterial blood pressure (BP). Inappropriate stimulation or deregulation of a cross talk among diverse vasomotor factors often contributes to or accounts for 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, pathophysiology, and function of the renal and systemic vasoactive systems with special emphasis on their role in the pathogenesis of hypertension in children.

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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 [1, 2]. The components of the RAAS are shown in Fig. 2.1. Renin cleaves its substrate, angiotensinogen (AGT), to generate Ang I

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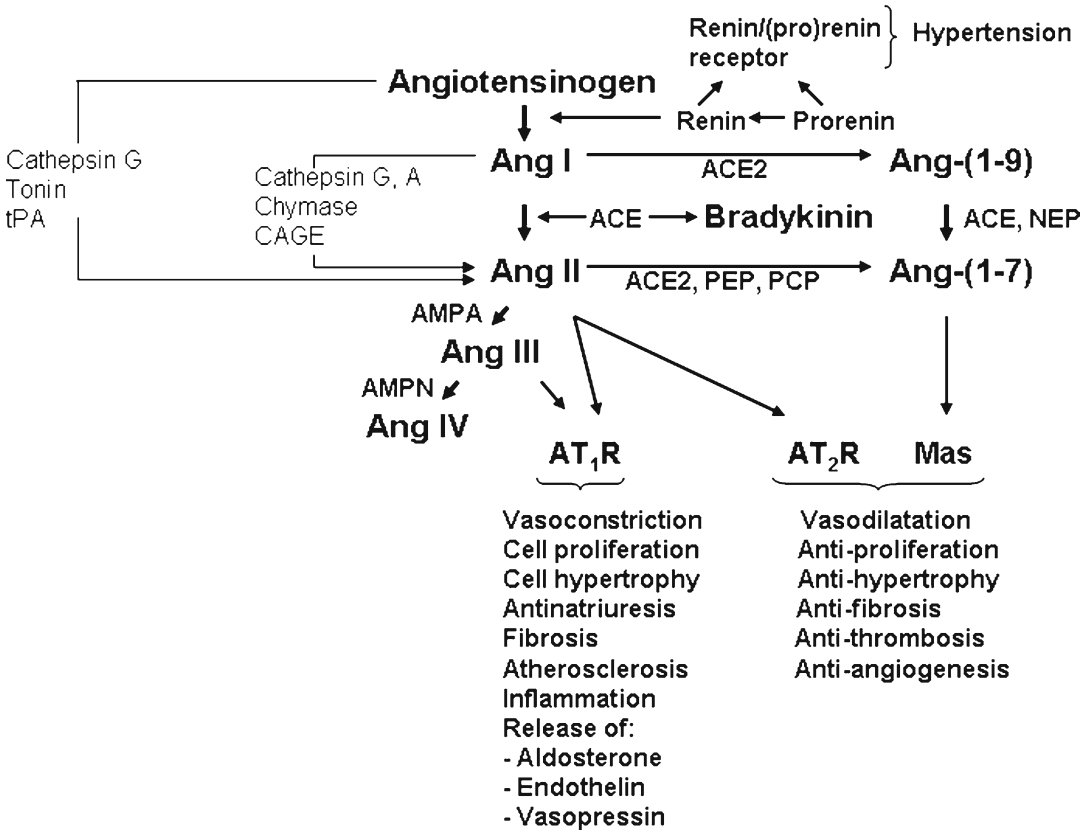

Fig. 2.1 The renin-angiotensin-aldosterone system. Ang II, angiotensin II; CAGE, chymostatin-sensitive Ang II-generating enzyme; AMPN, aminopeptidase N; tPA, tissue plasminogen activator

[Ang-(1-10)] (Fig. 2.1). 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 [3–5]. Most of hypertensinogenic actions of Ang II are attributed to the AT_1 receptor (AT_1R) [6]. Binding of prorenin to the (pro)renin receptor induces a conformational change of prorenin, facilitating the conversion of AGT to Ang I [7]. ACE2, a homologue of ACE, acts to promote Ang II degradation to the vasodilator peptide Ang-(1-7) [8, 9]. Ang-(1-7) acts via its cognate receptor, Mas, to counteract Ang II–AT_1R-mediated effects [10, 11].

Angiotensinogen

Angiotensinogen (AGT) is formed and constitutively secreted into the circulation by the hepatocytes [12]. In addition, AGT mRNA and protein are expressed in kidney proximal tubules, central nervous system, heart, adrenal gland, and other tissues [13, 14]. Although AGT is the only substrate for renin, other enzymes can cleave AGT to form Ang I or Ang II (Fig. 2.1) [15, 16]. Expression of the *AGT* gene is induced by Ang II, glucocorticoids, estrogens, thyroxine, and sodium depletion [14, 17, 18]. Importantly, A/G polymorphism at −217 in the promoter of the *AGT* gene appears to play a significant role in hypertension in African-Americans [19]. A significant association of a T704 → C (Met235 → Thr)

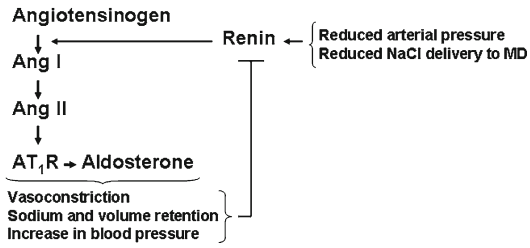

Fig. 2.2 Renin-angiotensin-aldosterone system in vasoconstriction, renal sodium, and water retention. Renin is secreted in response to reduced arterial pressure or NaCl delivery to macula densa (MD) and cleaves angiotensinogen to Ang I. Ang I is converted to Ang II by ACE. Ang II acts via the AT1 receptor (AT1R) 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

variant in exon 2 of the AGT gene with essential hypertension was reported in the cross-sectional study in Salt Lake City and Paris [20]. Recent meta-analysis indicated significant association between A-6G and A-20C polymorphisms in the AGT promoter and hypertension in the Chinese populations [21].

Prorenin, Renin, and (Pro)renin Receptor

Renin is synthesized as preprorenin in juxtaglomerular cells of the afferent arterioles of the kidney [22]. The human renin gene encoding preprorenin is located on chromosome 1 [23]. 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 [5, 24]. The kidney secretes both renin and prorenin into the peripheral circulation. Plasma levels of prorenin are approximately tenfold higher than those of renin [25]. 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. 2.2) [26–29]. 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) [30–32]. 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 [3, 33]. In addition, the circulating concentrations of AGT are more than 1,000 times greater than the plasma Ang I and Ang II levels [1]. Therefore, renin activity is the rate-limiting factor in Ang I formation from AGT [5]. Although Ang II can be generated from AGT or Ang I via renin/ACE-independent pathways [15, 16], the circulating levels of Ang II primarily reflect the consequences of renin action on AGT [34].

The renin/prorenin–(pro)renin receptor complex has emerged as a newly discovered pathway for tissue Ang II generation. In addition to proteolytic activation, prorenin may be activated by binding to (pro)renin receptor (PRR) [7].

The (pro)renin receptor (PRR) is expressed on mesangial and vascular smooth muscle cells and binds both prorenin and renin [35]. 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 [7]. 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 [36]. 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) [37–39]. Two single-nucleotide polymorphisms in the PRR gene (rs296815; rs5981008) were reported to be significantly associated with hypertension in adult Caucasians [40].

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. 2.1 and 2.3).

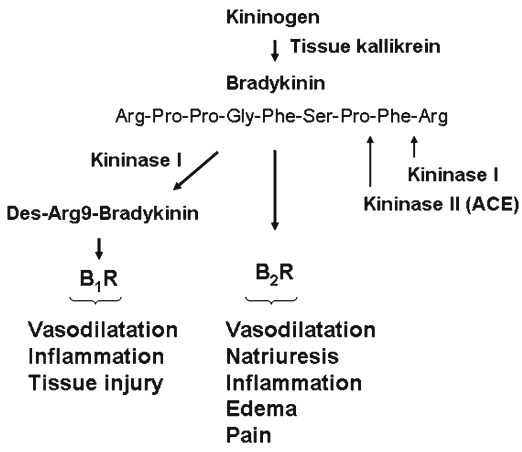

Fig. 2.3 The kallikrein–kinin system

There are two ACE isozymes, somatic and testicular, transcribed from a single gene by differential utilization of two distinct promoters [41]. Human somatic ACE contains 1,306 amino acids and has a molecular weight of 140–160 kilodaltons (kDa). In the kidney, ACE is present as ectoenzyme in glomerular vascular endothelial and proximal tubular cells [42]. 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 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 [43]. 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 [44]. 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 [45, 46]. 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 [47]. 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 (GPCRs): AT_1R and AT_2R. In rodents, AT_1R has two distinct subtypes, AT_{1A} and AT_{1B}, with greater than 95 % amino acid sequence homology [48]. In the kidney, AT_1R 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 [49]. Activation of the AT_1R increases BP in three ways: first, via direct vasoconstriction and increase in peripheral vascular resistance; second, by stimulation of Na^+ 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. 2.2) [50–52]. AT_1R activation also stimulates vasopressin and endothelin secretion, the sympathetic nervous system, and proliferation of vascular smooth muscle and mesangial cells [53–55]. The AT_2R has 34 % homology with AT_{1A} or AT_{1B} receptors [56]. AT_2R is expressed in the glomerular epithelial cells, proximal tubules, collecting ducts, and parts of the renal vasculature of the adult rat [57]. In contrast to AT_1R, AT_2R 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 [58–60]. In addition, the AT_2R promotes renal sodium excretion and inhibits proliferation in mesangial cells [58, 61, 62]. Thus, the AT_2R might oppose AT_1R-mediated effects on blood pressure, cardiovascular and renal growth, fibrosis, and remodeling, as well as RBF, fibrosis, and sodium excretion.

Angiotensin-Converting Enzyme 2

ACE2, a homologue 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) [8, 9]. Ang-(1-7) acts via the GPCR Mas encoded by the *Mas* proto-oncogene and counteracts Ang II–AT_1R-mediated effects [10, 11]. 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 [63, 64]. Although ACE2-null mice are normotensive and have normal cardiac structure and function, they exhibit enhanced susceptibility to Ang II-induced hypertension [65]. 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 [66]. 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 [67]. 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) [68].

Developmental Aspects of the RAAS

The developing metanephric kidney expresses all the components of the RAAS (Table 2.1). The activity of the renal RAAS is high during fetal and neonatal life and declines postnatally [69, 70]. Immunoreactive Ang II levels are higher in the fetal and newborn kidney than in the adult rat kidney [70]. The ontogeny of AT_1R and AT_2R mRNA in the kidney differs. AT_2R mRNA is expressed earlier than AT_1R, peaks during fetal metanephrogenesis, and rapidly declines postnatally [71, 72]. AT_1R mRNA expression increases during gestation, peaks perinatally, and declines gradually thereafter [71, 73]. ACE mRNA and enzymatic activity are expressed in the developing rat kidney, where they are subject to regulation by endogenous Ang II and bradykinin [70, 73]. In addition, the developing kidney expresses considerable ACE-independent Ang II-generating activity [15, 74], which may compensate for the low ACE levels in the early metanephros [70]. ACE2 mRNA and protein are expressed in the developing mouse kidney as early as on E12.5 [75]. Ang II, acting via the AT_1R, exerts a negative feedback on ACE2 in the developing metanephros.

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_1R, counteracts the vasodilator actions of bradykinin on the renal microvasculature of the developing rat kidney [76]. Premature infants exhibit markedly elevated PRA, which is inversely related to postconceptual age [77]. In healthy children, plasma renin activity (PRA) is high during the newborn period and declines gradually towards adulthood [78].

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 and renal failure and other abnormalities (e.g., hypocalvaria) in humans (Table 2.2) [43, 79]. 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_1R provides the foundation for the use of the classical RAAS inhibitors (ACE inhibitors and AT_1R 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

Table 2.1 Expression of the renin–angiotensin system components during metanephric kidney development

	E12	E14	E15	E16	E19	References
AGT						
Mouse:	UB, SM	UB, SM, PT				[178]
			Rat: UB, SM	UB, SM, PT	PT	[179]
Renin						
Mouse: precursor cells present M of entire kidney M, close to V and G V, G						[180]
			Rat: V	V	V	[69]
ACE						
				Rat: PT, G, CD		[181]
ACE2						
Mouse		UB, G, PT		PT		[75]
AT_1						
Mouse:	UB, M	UB, G	UB, V	PT, UB, SM, G	PT, DT	[178]
						[73]
			Rat: G, UB, SM	SM	PT, CD, G	[71]
AT_2						
Mouse:	MM	MM, SM		Medullary SM, under renal capsule		[73]
		Rat: MM		Condensed M	Medulla, G, V	[71]

AGT angiotensinogen, *ACE* angiotensin-converting enzyme, *ACE2* angiotensin-converting enzyme 2, AT_1/AT_2 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

plasma renin activity [80]. Recent availability of a direct inhibitor of (pro)renin receptor offers new possibilities in antihypertensive therapy in children that remain to be explored [81].

Aldosterone

Ang II, acting via the AT_1R, stimulates an increase in transcription and expression of the rate-limiting enzyme in the biosynthesis of aldosterone and CYP 11B2 (aldosterone synthase) in the zona glomerulosa of the adrenal glands [50]. Aldosterone stimulates reabsorption of Na^+ and secretion of potassium by principal cells in the collecting duct. In turn, retained Na^+ is responsible for increased extracellular fluid volume that increases BP. Secretion of aldosterone is stimulated by high plasma potassium concentration and adrenocorticotropic hormone (ACTH) and inhibited by atrial natriuretic peptide (ANP) [82–84]. Aldosterone-dependent Na^+ reabsorption is due to upregulation of epithelial Na^+ channel-α (alfa) (ENaCα (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 [85]. Aldosterone downregulates the expression of histone H3 methyltransferase Dot1a and the DNA-binding protein Af9 complexed with chromatin within the ENaCα (alfa) 5'-flanking region [86]. 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 *ENaCα*b 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 offer survival benefits in heart failure and augment potential for renal protection in proteinuric chronic kidney disease.

Table 2.2 Effect of genetic inactivation of the renin–angiotensin system genes in mice on the renal and blood pressure phenotype

Gene	Function of gene	Renal phenotype	Blood pressure	References
AGT	Renin substrate	Vascular thickening	Very low	[168, 170]
		Interstitial fibrosis		
		Delayed glomerular maturation		
		Hypoplastic papilla		
		Hydronephrosis		
		Reduced ability to concentrate urine		
Renin	Enzyme that generates ANG I from AGT	Arterial wall thickening	Very low	[171]
		Interstitial fibrosis		
		Glomerulosclerosis		
		Hypoplastic papilla		
		Hydronephrosis		
ACE	Enzyme that generates ANG II from ANG I	Arterial wall thickening	Very low	[172]
		Hypoplastic papilla and medulla		
		Hydronephrosis		
		Reduced ability to concentrate urine		
$AT_{1A/B}$	Ang II receptor	Decreased kidney weight	Very low	[173, 174]
		Delayed glomerular maturation		
		Arterial wall thickening		
		Interstitial fibrosis		
		Tubular atrophy		
		Hypoplastic papilla and medulla		
		Hydronephrosis		
		Reduced ability to concentrate urine		
AT_{1A}	Ang II receptor	Normal or mild papillary hypoplasia	Moderately low	[6]
AT_{1B}	Ang II receptor	Normal	Normal	[175]
AT_2	Ang II receptor	Duplicated ureters	High	[176, 177]
		Hydronephrosis		

Glucocorticoids

Glucocorticoids are vital for normal development and control of hemodynamic homeostasis. Cortisol or dexamethasone infusion increases BP in the fetal sheep [87, 88]. Dexamethasone increases BP in wild-type serum and glucocorticoid-inducible kinase (Sgk) $Sgk1^{+/+}$ mice but not in $Sgk1^{-/-}$mice [89], 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 [90], 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 [91]. 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 kininogenase tissue kallikrein [92] (Fig. 2.3).

Bradykinin is degraded by ACE–kininase II, the enzyme that also converts Ang I to Ang II [93]. Kinins act by binding to B1 (B_1R) and B2 (B_2R) receptors. The B_1R is activated by Des-Arg^9-BK produced from BK by kininase I and mediates tissue injury and inflammation [94]. 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 [95]. Following completion of nephrogenesis, kininogen is localized in the collecting duct. The main kininogenase, true tissue kallikrein, is encoded by the *KLK1* gene [96]. 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 [95].

In the developing rat kidney, kallikrein mRNA and immunoreactivity are present in the connecting tubule [97]. In the mature kidney, tissue kallikrein mRNA is expressed in the distal tubule and glomeruli [98]. 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 [99]. 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 [100]. The human *B_1R* and *B_2R* genes are located on chromosome 14 and demonstrate 36 % genomic sequence homology [101]. Both B_1R and B_2R are members of the seven-transmembrane GPCR family. During metanephrogenesis, the B_2R is expressed 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 [102]. 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 [94]. 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_1R [76]. Stimulation of the B_2R during adult life stimulates production of nitric oxide and prostaglandins resulting in vasodilation and natriuresis [99]. 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 [100]. Moreover, *B_2R*-null mice are prone to early onset of salt-sensitive hypertension [103]. Interestingly, B_1R receptor blockade in *B_2R*-null mice produces a significant hypertensive response [104], 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 [105]. 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 [106].

Arginine Vasopressin

Arginine vasopressin (AVP), also known as antidiuretic 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 [107]. In adult species, AVP supports arterial BP when both the sympathetic system and the RAAS are impaired by sympathetic blockade [108]. Treatment with a V_1R antagonist has no effect on arterial BP in fetal sheep [109, 110]. In contrast, antagonism of the V_1R during hypotensive hemorrhage impairs the ability of the fetus to maintain BP [111]. 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.

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 [112]. The major source of NO production in the rat kidney is the renal medulla, where NO regulates medullary blood flow, natriuresis, and diuresis [113, 114]. NO promotes pressure natriuresis via cGMP [115]. The effects of Ang II or AVP on medullary blood flow are buffered by the increased production of NO [113], 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 [115], 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 [116]. In fetal rat kidneys, endothelial NO synthase (eNOS) immunoreactivity is first detected in the endothelial cells of the intrarenal capillaries on E14 [117]. These findings suggest that eNOS may play a role in regulating renal hemodynamics during fetal life. Moreover, eNOS-knockout mice exhibit abnormal aortic valves and congenital atrial and ventricular septal defects, indicating that eNOS-derived NO plays an important role in the development of the circulatory system [118]. 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 [119]. 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 [120, 121].

Asymmetrical Dimethylarginine

Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of eNOS [122]. Infusion of ADMA increases BP and renal vascular resistance and decreases renal plasma flow during adulthood [123]. ADMA levels in fetal umbilical venous plasma are higher than in maternal plasma [124]. 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 normotensive children in one study [125]. In contrast, plasma ADMA levels did not differ between normotensive and hypertensive young adults [126]. Moreover, plasma ADMA correlates negatively with vascular resistance [126], 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 [127, 128]. 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_A and ET_B GPCRs. In the kidney, ET-1 mRNA is expressed in the glomeruli and medullary collecting ducts [129, 130]. ET receptors are located in podocytes, glomeruli, afferent and efferent arterioles, proximal tubule, medullary thick ascending limb, and collecting duct [131]. Activation of the ET_B receptor results in natriuresis and vasodilation via release of NO and PGE_2, whereas the ET_A receptor mediates renal vasoconstriction [132]. In the fetal lamb, ET_A and ET_B receptors expressed on vascular smooth muscle cells mediate vasoconstriction, whereas ET_B receptors located on endothelial cells mediate vasodilation [133, 134]. In the renal circulation of fetal sheep, ET-1, acting via the ET_B receptor, results in vasodilation [135]. However, ET_A receptor-mediated vasoconstriction also contributes to the regulation of the fetal renal vascular tone [136]. The critical role for the renal ET-1 and ET_A/ET_B 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_A and ET_B receptors [137, 138]. Moreover, BP in these knockouts increases further with high salt intake, indicating that combined ET_A/ET_B 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) [139–142]. Natriuretic peptides act through binding to three guanylyl cyclase-linked receptors: NPR-A, NPR-B, and NPR-C [143]. 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 [143, 144], and are rapidly degraded in the lung and kidney by neutral endopeptidase [145]. 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, a decrease in BP, and intravascular fluid volume [146]. 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 [147–149]. 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 [148, 150]. Infusion of ANP into the circulation of the lamb fetus decreases BP and causes diuresis [151]. 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 [150, 152]. Plasma levels of ANP are higher in preterm as compared with term infants [153]. In full-term infants, circulating ANP levels increase during the first week of life and decrease thereafter [154]. 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 [155], ANP-null mice develop hypertension later in life [156]. 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 [156, 157].

Vasoactive Factors and Developmental Programming of Hypertension

An inverse relationship between birth weight or maternal undernutrition and adult BP led to the concept of developmental programming of hypertension ([158], and Chaps. 1, 2, 3, 4, 5, 6, and 7). 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 [159, 160]. 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 $AT_{1B}R$ in offspring in the rat [161]. It is conceivable that epigenetic modifications of $AT_{1B}R$ gene may 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 [162–164]. In addition, heterozygous eNOS offspring of *eNOS*-null mothers exhibit impaired endothelium-dependent vasodilation as compared to heterozygous offspring of $eNOS^{+/+}$ mothers [165]. 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 impact vasoactive factor systems and their interplay to program hypertension during postnatal life.

Renalase

Renalase, an amine oxidase expressed in the kidney, heart, liver, and brain, metabolizes catecholamines [166, 167]. Anesthetized BP and heart rate are reported as higher in renalase null as compared to wild-type littermates [158]. Available data suggest that renalase deficiency is associated with increased sympathetic tone and resistant hypertension. Further, recombinant renalase is a potent antihypertensive agent that has some promise as a potential option for treating hypertension in chronic kidney disease [167].

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 improves our understanding of the developmental origin of hypertension and cardiovascular disease and helps 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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Cardiovascular Influences on Blood Pressure

3

Albert P. Rocchini

Abstract

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 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), and this chapter discusses the important factors that regulate both cardiac output and systemic vascular resistance.

Keywords

Blood pressure homeostasis • Afterload • Contractility • Preload

Introduction

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

Based on Ohm's law for fluids [1], blood flow through any tissue is equal to the pressure gradient across the tissue divided by the vascular resistance of that tissue or organ. For the cardiovascular system on a macro-level, Ohm's law for fluids would state that whole-body flow (cardiac output (CO)) is equal to driving pressure (mean arterial blood pressure (MBP) minus mean venous pressure divided by vascular resistance of the whole body (systemic vascular resistance (SVR)). However, since mean venous pressure is relatively small, it is usually omitted.

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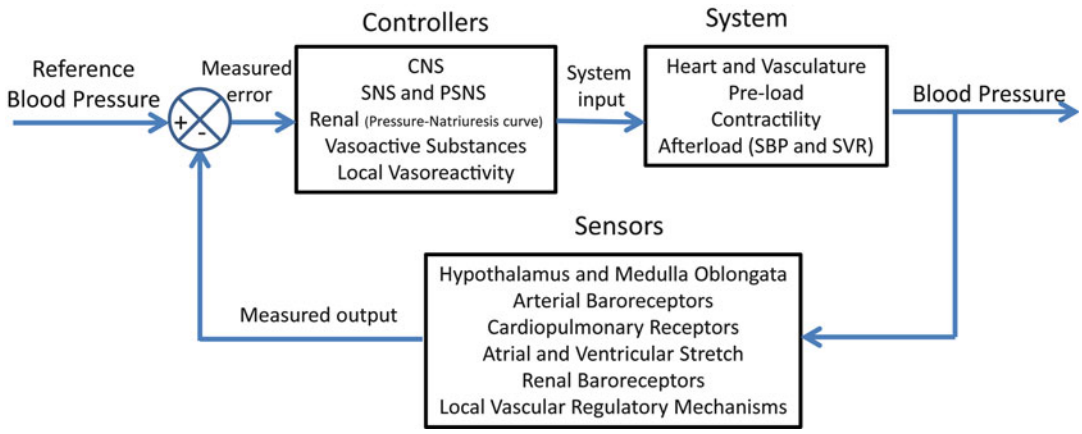

Fig. 3.1 A schematic illustration of a closed feedback loop to control mean arterial pressure (MAP) around a reference level (set point). The reference (basal MAP) is defined as the external input of the system. The controllers (physiological determinants of MAP) manipulate the inputs to the system (heart and vasculature) to obtain the desired effect on the system output (MAP). The sensors (physiological 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. (*CNS* central nervous system, *SNS* sympathetic nervous system, *PSNS* parasympathetic nervous system, *SVR* systemic vascular resistance, and *SBP* systolic blood pressure)

Ohm's Law for the Cardiovascular System:

$$CO = \frac{MBP}{SVR}$$

The local control of tissue and organ flow (autoregulation) involves both short- and long-term mechanisms. The short-term mechanisms can be activated within seconds resulting in vasoconstriction or dilatation 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 thickening or thinning of vessel walls and/or decreasing or increasing the number of capillaries. Since regional blood flows are difficult to measure clinically, differ widely, and in some cases vary greatly, 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 [2].

Blood pressure homeostasis is accomplished through a closed negative feedback loop. Figure 3.1 schematically depicts the concept of a closed negative feedback loop [3]. The loop is negative, because the sensed value is subtracted from the desired value (reference value) to create an error signal, which is then applied to return the system to its reference level. For blood pressure homeostasis, the controllers are the determinants of mean arterial pressure, the system is the heart and vasculature, and the sensors are the physiological monitors of the system output (systemic 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.

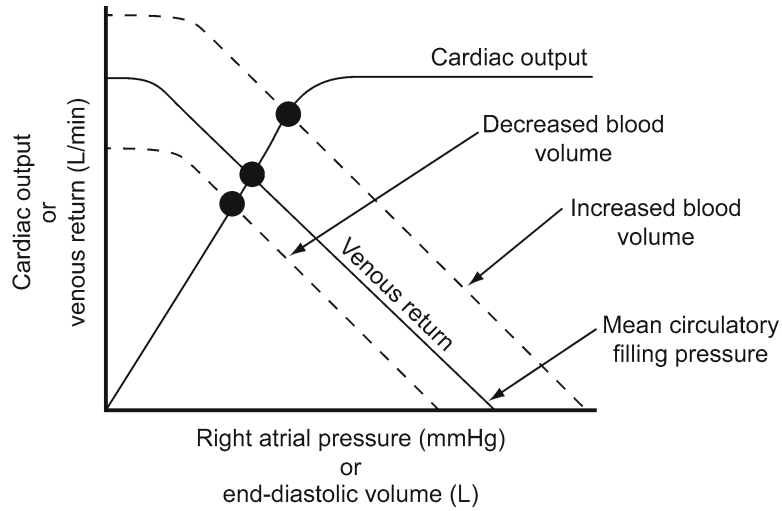

Fig. 3.2 Graphic analysis of Guyton's classic cardiac function curve and the venous return curve. The graph consists of simultaneous plots of cardiac output and venous return as a function of left ventricular end-diastolic volume or right atrial pressure. The *solid dot* represents the steady state where 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 curve 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 [5])

Cardiac Output

Three of the major determinants of cardiac output are preload, contractility, and afterload. Preload, contractility, and afterload are discussed in this section.

Preload

From a clinical standpoint, preload is defined as ventricular end-diastolic volume/pressure or atrial filling pressure. The Frank-Starling mechanism [4] describes the ability of the heart to increase its cardiac output as end-diastolic volume increases (Fig. 3.2). 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 Fig. 3.2). Venous compliance can be acutely effected 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, and α-receptor blockers) 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 increases cardiac output. The exercise-induced decrease in venous compliance occurs since the major veins in the limbs and abdomen are situated between skeletal muscles. When the skeletal muscles contract and relax, they compress these 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 [6].

Circulating Blood Volume

Long-term changes in preload are caused by changes in circulating blood volume. From the hearts 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 (release is stimulated by distention of the atria and ventricles).

Cardiopulmonary Baroreceptors

The cardiopulmonary baroreceptors are comprised 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 (see Chaps. 1 and 2). 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 [7]. Brain natriuretic peptide is a 32-amino acid peptide that was originally identified in the brain but is predominately located within the cardiac ventricles. The stimuli for release of both peptides are atrial or ventricular distention and stretch, sympathetic stimulation of β-adrenoceptors, angiotensin II, and endothelin [8]. 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 which phosphorylates proteins that produce the following physiological responses: in the kidney it dilates afferent glomerular arterioles resulting in increased glomerular filtration rate, it decreases sodium reabsorption in the distal convoluted tubule and cortical collecting ducts which results in a greater excretion of sodium and water, and it decreases renin release; in the adrenal gland it reduces aldosterone secretion; in the vascular system it relaxes vascular smooth muscle in arterioles and venules; and in adipose tissue it increases 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 circulation natriuretic peptide levels [9]. From a clinical standpoint, brain natriuretic peptide (BNP) is useful from both a diagnostic and therapeutic standpoint. For patients with congestive heart failure, BNP levels are usually greater than 100 pg/ml [10]. A recombinant form of BNP (nesiritide) has been used to treat refractory congestive heart failure [11].

The Kidney and Blood Volume

Changes both in autonomic tone and natriuretic peptide levels affect the control of salt and water excretion by the kidney. In most clinical situations, both short- and long-term changes in preload are regulated based on the relationship of urinary sodium excretion as a function of arterial pressure (pressure-natriuresis relationship) [12, 13]. Figure 3.3 depicts the relationships 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 intakes, adjustments in the pressure-natriuresis curve occur (left shift with a high salt intake and right shift with a low salt intake) allowing the

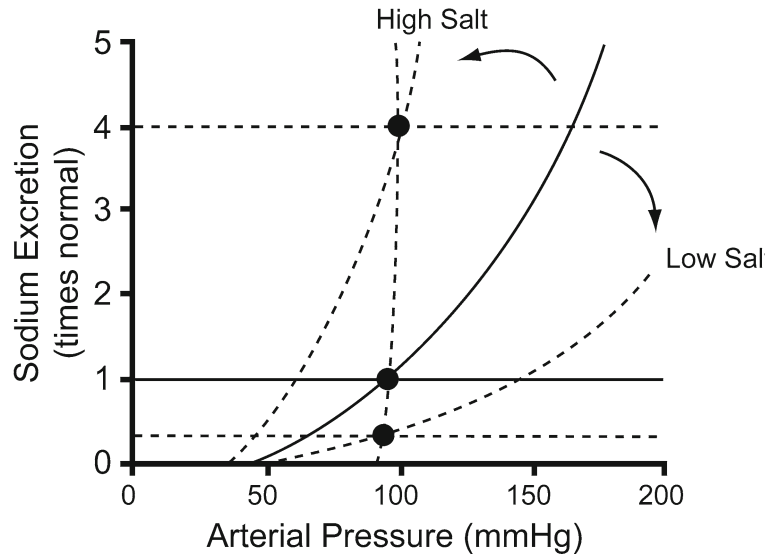

Fig. 3.3 Graphic representation of the concept of renal pressure-natriuresis and how adjustments of this relationship are affected by changes in salt intake. The *solid dots* represent the equilibrium point between mean arterial pressure and salt excretion. The *solid middle curve* represents the pressure-natriuresis 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 [5])

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. In addition, it is important to remember that the dietary salt-induced changes in the pressure-natriuresis curve 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 that occurs as a consequence of a chronic increase in circulating blood volume leads to systemic hypertension. For example, the hypertension associated with obesity is in large part believed to be related to a chronic change in the renal pressure-natriuresis relationship which leads to a chronic increase in circulating blood volume, cardiac preload, and cardiac output [14]. Similarly, end-stage renal disease is also associated with chronic volume expansion and hypertension.

Cardiac Contractility

The second determinant of cardiac output is 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 [1]. The degree of binding that occurs is directly related to the intracellular concentration of calcium. The heart normally changes its contractile state through modulation of the sympathetic nervous system. Increased sympathetic tone results in the release of catecholamines (norepinephrine and epinephrine)

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 (e.g., norepinephrine, epinephrine, dopamine, dobutamine, milrinone)

Chronic Changes in Cardiac Contractility and Hypertension

A primary increase in cardiac output may be the antecedent of essential hypertension. In 1957, Widimsky et al. [15] reported that cardiac output was significantly increased in a group of young patients with borderline hypertension, an observation confirmed by others [16–19]. Julius [20] 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 et al. [20–22] also 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 continued pharmacologic parasympathetic, beta- and alpha-adrenergic inhibition normalizes the blood pressure. Stern et al. [23] showed that persons with hyperdynamic physiology 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 (σ) where

$\sigma \propto \frac{P.r}{h}$ (P, systolic ventricular pressure; r, radius of the ventricle; and 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 used in 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 [24]. 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. [25] 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 heart failure.

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 [26]. In young persons, the thoracic aorta contains a predominance of elastin over collagen; however, 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 in normal children and adolescents one usually finds that leg systolic blood pressure is higher 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 [27]. 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 [28–31]. In fact, because the traditional end points of stroke, myocardial infarction, and mortality used in studies of adults are unsuitable to evaluate the risk and benefits of pediatric clinical trials, pulse wave velocity has been recommended as a useful marker for predicting future cardiovascular disease in pediatric populations [31, 32].

Systemic Vascular Resistance

In the absence of aortic stenosis and aortic coarctation, systemic vascular resistance is the major determinants 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 or organ blood flow is regulated by several factors including metabolism, myogenic responses, and the endothelial release of relaxing factors [33]. 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 [34], 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 specialized 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) [35, 36].

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 decreased 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 [36, 37]. 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 [38].

The final major mechanism for the local control of regional organ or 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 of the major mechanisms for their release is vascular shear stress [39]. 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 [40].

Autonomic Nervous System Control of Vascular Resistance

Short- and long-term control of arterial pressure involves both the sympathetic and parasympathetic 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, and cardiac atria and ventricles. A discussion of the low-pressure (cardiopulmonary) receptors can be found in the preload 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 [41, 42]. 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 [43]. In chronic hypertension the baroreceptors are reset to the higher pressure, and baroreceptor activity returns to near-normal levels. However, the baroreceptors become less sensitive, that is, the slope of the arterial pressure-activity curve is decreased [44, 45].

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 [44]; however, recent research has suggests that the baroreceptors do contribute to long-term control of blood pressure. Lohmeier et al. [46] demonstrated that sustained activation of the central baroreceptors plays an important role in the pathogenesis of obesity-related hypertension. He and others [47, 48] demonstrated that chronic stimulation of the carotid sinus results in lowering of blood pressure in both experimental obesity-related 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 while increasing fractional sodium excretion [49].

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) and modulate arterial pressure through regulation of vasopressin secretion [50].

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 creating lesions in the posterior hypothalamus, whereas stimulation in this region intensifies the hypertension [51]. 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 lead to a decrease in food intake and an increase in energy expenditure, induced in part, via the precursor peptide pro-opiomelanocortin (POMC) [52]. Leptin, a 167-amino acid hormone that is secreted exclusively by adipocytes, activates POMC-containing neurons to inhibition of food intake and activation of the sympathetic nervous system [53]. 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 [54]. In obese melanocortin-4 receptor-deficient humans, Greenfield et al. [55] 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 melantocortin-4 receptor agonist for 7 days caused significant increases in blood pressure [55]. Sayk et al. [56] demonstrated that in obese persons who carry melanocortin-4 receptor mutations, there is an inverse relationship between obesity and muscle sympathetic nerve activity. Finally, Lohmeier et al. [46] demonstrated in dogs with obesity-related hypertension, 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 substances is a major modulator of systemic vascular resistance. Other than the catecholamines that are released by either the sympathetic nervous system or adrenal gland, three other important sources of vasoactive substances are the renin-angiotensin-aldosterone system (angiotensin II), endothelin, and vasopressin.

The Renin-Angiotensin-Aldosterone System

Renin is synthesized, stored, and released by the juxtaglomerular cells of the kidney and is the rate-limiting enzyme in the biochemical cascade that forms angiotensin II, a potent vasoconstrictor (see also Chaps. 1 and 2). Physiological regulation of renin release is modulated by the renal baroreceptors, macula densa, and renal nerves. The renal baroreceptor in the afferent glomerular arterioles 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 changes in distal tubular sodium delivery. A decrease in sodium delivery leads to an increase in renin synthesis and release. Finally, the renal sympathetic nerves directly innervate the juxtaglomerular cells, and stimulation of these nerves causes renin release. Renin cleaves the decapeptide, angiotensin I (Ang I), from angiotensinogen, and angiotensin converting enzyme converts Ang I to angiotensin II (Ang II), a potent vasoconstrictor. Ang II binds to two transmembrane receptors, angiotensin II receptor subtype I (AT1) and angiotensin II receptor subtype II (AT2), which mediate its physiological actions. Activation of AT1 results in blood vessel constriction, secretion of aldosterone, amplification of sympathetic nervous system outflow, increased renal sodium retention, and the stimulation of cellular growth in the cardiovascular system. Activation of the AT2 receptor opposes the actions of the AT1 receptor, in that it promotes vasodilation, induces apoptosis, and promotes natriuresis [57]. Other recently described components of the renin-angiotensin-aldosterone system are described in Chaps. 1 and 2.

Endothelin and the Cardiovascular System

Endothelin, 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 [58].

Vasopressin and Hypertension

Vasopressin, or antidiuretic hormone, a peptide 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 [59].

Summary

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

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Ion and Fluid Dynamics in Hypertension

4

Avram Z. Traum

Abstract

The role of ion transport in hypertension has been the focus of much investigation, and manipulation of ion transport is utilized therapeutically. However, the mechanisms behind sodium flux that lead to hypertension are not well understood. Target proteins and diuretic agents, monogenic forms of hypertension, and genetic disorders of renal salt wasting have all provided insight into these pathways. This chapter reviews some of the channels involved in blood pressure regulation and their relevance to human hypertension.

Keywords

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

Among the many determinants of blood pressure, the role of ion transport has played a key role in both the basic understanding and clinical management of hypertension. For decades, clinicians have counseled their hypertensive patients to limit salt intake. This approach has been codified in clinical guidelines and forms the backbone of what has been termed therapeutic lifestyle modifications [1, 2]. Sodium restriction has been studied in clinical trials as an effective measure for control of moderately elevated blood pressure [3, 4]. In addition to sodium restriction, the role of natriuresis has been translated into therapy, as thiazide diuretics have assumed the role of first-line pharmacologic therapy for hypertension in adults [5, 6].

At a more basic level, an expanding list of genes has been implicated in monogenic forms of hypertension. Such genes typically encode proteins that affect renal tubular sodium handling (reviewed in Chap. 6). Moreover, mutations leading to renal salt wasting, as observed in Bartter and Gitelman syndrome, are associated with normal and low blood pressure.

While monogenic conditions associated with high or low blood pressure provide insight into the pathogenesis of hypertension, such entities

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comprise only a small fraction of the overall burden of hypertension. More broadly, however, pathogenic changes in ion transport have been implicated in both animal models 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 the function and structure of some of the ion channels studied in hypertension and their relevance to clinical practice.

Sodium Channels

Given the importance of salt in the management of blood pressure, sodium channels have been extensively studied as targets in both animal models of hypertension and 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^+/H^+ exchangers (NHEs), the Na^+-K^+-$2Cl^-$ cotransporter (NKCC), the Na^+-Cl^- cotransporter (NCC), as well as the epithelial sodium cotransporter (ENaC), and the sodium-potassium ATPase (Na^+/K^+ ATPase). These are listed in Table 4.1.

NHE Transporters

Na^+/H^+ transporters (also called antiporters) 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 at least nine NHEs; the NHE1 transporter is ubiquitous, while NHE3 is highly expressed in the kidney [7]. 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).

Table 4.1 Sodium Transporters along the Renal Tubule

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

TAL thick ascending limb of the loop of Henle

NHE1 activity is increased in the SHR in multiple cell types, including RBCs, platelets, leukocytes, skeletal muscle, vascular smooth muscle cells, and tubular epithelial cells. Na^+/H^+ transport in red blood cells (RBCs) has been examined in humans as well and appears to correlate with renal sodium retention in hypertensive subjects [8]. The human studies align well with the differential effect in SHR versus MHS strains, as approximately half the patients studied had increased RBC Na^+/H^+ activity [9, 10]. This increased Na^+/H^+ activity likely reflects a systemic effect, as it has also been demonstrated in skeletal muscle in both SHR [11] and in humans with essential hypertension [12].

In contrast to NHE1, the related NHE3 transporter has a more restricted distribution that includes the proximal tubule, and RBC expression of NHE3 has not been reported. In SHR, NHE3 activity is increased [13], though mRNA expression is not altered. However, this enhanced activity may be related to decreased expression of the NHE regulatory factor 1 (NHERF1) [14], which normally inhibits the activity of NHE transporters, suggesting that changes in NHE3 activity are unrelated to gene expression or structure per se. Kelly et al. [15] studied the relative contributions to sodium transport by NHE1 and NHE3 in proximal tubule cells in the SHR as compared to their control, the Wistar-Kyoto (WKY) rat. Their studies revealed equal activity of both proteins. While NHE1 protein expression was similar to that of the normotensive WKY, NHE3 expression was increased by 50 % in the SHR. An earlier study [16] in the *NHE3* knockout mouse demonstrated proximal renal tubular acidosis with salt wasting, polyuria, and lower blood pressure, in spite of increased renin mRNA

expression and plasma aldosterone levels. These mice also demonstrated diarrhea related to decreased intestinal expression of NHE3, the other major site of expression.

Human studies on NHE3 in hypertension are limited. Zhu et al. [17] studied polymorphisms in the gene encoding NH3, also known as solute carrier family 9 member (*SLC9A3*), 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 the six polymorphisms studied was associated with hypertension, although only a subset of the gene sequence was interrogated. Further, there were no validation sets to confirm the reported associations.

NKCC Transporters

The sodium-potassium-chloride cotransporter (NKCC, *SLC12A2*) 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, 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 [18, 19]. 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, [20] a severe form of Bartter syndrome heralded by antenatal manifestations with polyhydramnios, prematurity, and postnatal electrolyte wasting and volume depletion. Biochemically, the hallmark of all forms of Bartter syndrome is elevated plasma renin activity and aldosterone level with low to normal blood pressure. Perhaps more generally relevant are studies by the same group on subjects in the Framingham Heart Study that identified mutations in genes encoding NKCC2, as well as the sodium-chloride cotransporter (NCCT), and the renal outer medullary potassium channel (ROMK), all of which appeared to be protective against hypertension [21].

Similar to NHE transporters, NKCC has also been studied in RBCs both in animal models and in humans with hypertension. There is higher activity in RBCs in MHS rats compared to controls (the Milan normotensive strain, or MNS), and these animals demonstrate a greater natriuretic response to bumetanide [22]. Since this strain has normal expression of NKCC2 mRNA and protein [23], 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 this finding accounts for only a fraction of those with low-renin hypertension [24–26]. However, patients with higher NKCC1 levels also have an exaggerated response to furosemide [27].

The NCCT

Given the widespread use and success of thiazides in treating essential hypertension, the sparse data on the sodium-chloride cotransporter (NCCT) in both animal models and human hypertension is surprising. Capasso et al. demonstrated increased expression of the NCCT in MHS rats, in contrast to NKCC2 and NHE3 mRNA expression, which were not increased [23]. Mutations in the *NCCT* gene (*SLC12A3*) were also found to be protective against the development of high blood pressure in Framingham Heart Study subjects [21]. 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 [28].

ENaC

Activating mutations in genes encoding the epithelial sodium channel (ENaC) cause Liddle syndrome, probably the best known monogenic form of hypertension (see also Chap. 6). 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 down-regulated 4-2 (Nedd4-2) [29]. The putative role of the 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. Early studies in primary cultures of collecting ducts from this strain, sodium transport was enhanced as compared to the Dahl salt-resistant strain and was augmented by aldosterone and dexamethasone, suggesting that either ENaC or Na^+/K^+ ATPase must have been involved [30]. In follow-up experiments to distinguish between whether the effect was due to ENaC or to Na^+/K^+ ATPase, sodium transport was unaffected by ouabain, which inhibits the Na+/K + ATPase, suggesting increased ENaC activity as the cause [31].

As noted, Liddle syndrome is caused by mutations in the genes encoding the ß- and γ-subunits of ENaC. These mutations result in truncated proteins lacking the C-terminal end, a segment that is essential for intracellular regulation. The mutations 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 ß-ENaC variants in hypertensive families [32]. After determining the most common changes observed in the last exon, they assessed the frequency of these variants 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 the various constructs were studied in *Xenopus* oocytes [32].

A relatively common variant in ß-ENaC, T594M, has been examined in a number of studies. This variant was first reported by Su et al. [33] 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 [34]. A second study identified an association between this same variant and hypertension in 348 blacks in a study from the UK [35]. 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 [36]. Moreover, administration of amiloride to those with this variant did not demonstrate any differential effect as compared to those with wild-type ß-ENaC. Thus, the role of ENaC variants in essential hypertension remains incompletely elucidated.

Na^+/K^+ ATPase

The ubiquitous sodium-potassium ATPase (*Na^+/K^+ ATPase*) 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 in the length of the renal tubule [37]. Earlier studies revealed increased Na^+/K^+ ATPase activity in kidney extracts from the Milan hypertensive rat as compared with its normotensive control [38]. This phenomenon was due to increased activity of the pump per se, as pump number was not increased, as assessed by the number of ouabain binding sites [39].

In contrast to primary overactivity of this pump, Blaustein et al. [40] have proposed an alternative model based on an unidentified endogenous ouabain-like substance. They hypothesize that salt retention leads to production of this ouabain-like substance, which then increases vasomotor tone due to the linked effects of the Na^+/K^+ ATPase and calcium flux [41]. 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 [42]. An endogenous ouabain-like substance has been isolated from the MHS hypothalamus [43].

Calcium Flux

As noted, sodium and calcium flux are interrelated, most notably due to the effects of the Na^+/K^+ ATPase and cross talk with the Na^+/Ca^{2+} exchanger (NCX). This effect has been harnessed therapeutically with the use of digoxin to increase myocardial contractility. Inhibition of the Na^+/K^+ ATPase leads to an increase in intracellular sodium levels with secondary redistribution of calcium due to NCX [44]. The resulting rise in intracellular calcium improves contractility in cardiac myocytes and vascular smooth muscle cells (VSMCs). This link has been further established at a cellular compartment level with studies that show colocalization of Na^+/K^+ ATPase and NCX [40, 45].

It should be noted that differing Na^+/K^+ ATPase subtypes have different affinity for ouabain; α2 subtypes have the greatest affinity for endogenous ouabain and may mediate its effect on VSMCs [46, 47]. In mice, expression of the α2 subtype with a shortened N-terminus is dominant negative for expression of wild-type full-length α2 pump [48]. When this dominant-negative α2 pump was expressed using a smooth muscle-specific myosin promoter, reduced pump function and elevated blood pressure were observed [40]. Conversely, mice that overexpress the α2 pump within smooth muscle have significantly lower blood pressure than either α2 wild-type mice or mice with α1 overexpression [49].

The relationship between the Na^+/K^+ ATPase and NCX transporters suggests a sequence by which increased salt and water intake leads to volume expansion, followed by secondary release of endogenous ouabain [40, 50]. The inhibition of the Na^+/K^+ ATPase acts to prevent further sodium retention by the kidneys. Within VSMCs, Na^+/K^+ ATPase inhibition enhances calcium exchange via NCX with a resultant increase in intracellular calcium and vasoconstriction. Furthermore, because of membrane depolarization related to Na^+/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 α2 pump as described above lead to increased vascular tone. However, the α1 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 that are present in the given tissue. As noted, ouabain inhibits the α2 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 α1 pump via stimulation of epidermal growth factor receptor and subsequent phosphorylation and activation of the α1 pump [51, 52]. Thus, the differential effect on isoforms of the Na^+/K^+ ATPase leads to a net increase in blood pressure [53].

Perhaps the most exciting outgrowth of this research is the development of an inhibitor of the Na^+/K^+ ATPase for the treatment of hypertension. Rostafuroxin (PST 2238) is a sterol compound that competitively binds to Na^+/K^+ ATPase and inhibits the effects of ouabain. In MHS rats, rostafuroxin lowered blood pressure compared to vehicle. This effect was also seen in Sprague-Dawley rats treated with ouabain, deoxycorticosterone acetate, and salt-treated rats in a remnant kidney model [53–55]. One recent phase II study in hypertensive humans showed no effect of five different doses on blood pressure lowering [56]. However, when patients were stratified by genotype, rostafuroxin was associated with a significant drop in blood pressure [57]. 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 or hydrochlorothiazide [58].

Regulation of Ion Flux

While multiple channels have increased activity that leads to heightened net sodium reabsorption and hypertension in both animal and human studies, the exact mechanism remains unclear. The transporters studied generally do not have increased levels of mRNA or protein, and the association studies for specific polymorphisms of the involved transporters have provided

conflicting data. However, the cytoskeleton has been implicated as having a role in increased functional sodium resorption. For example, adducin, briefly discussed above, is a ubiquitously expressed component of the cytoskeleton. Adducin is found in both rats and humans, and its association with salt-sensitive hypertension has been described in both.

Bianchi et al. reported that adducin mutations in both α- and β-subunits were associated with hypertension in MHS rats [59]. A subsequent study by those investigators showed that in rat renal tubular epithelium, adducin mutations increase Na^+/K^+ ATPase activity [60]. They later described that MHS rats with adducin mutations did not have the expected endocytosis of Na^+/K^+ pumps in response to dopamine [61] and that the lack of endocytosis of the Na^+/K^+ ATPase may reflect a broader alteration in clathrin-dependent endocytosis [62]. Other groups have shown that in a variety of rat models of hypertension, genes encoding adducin subunits are located within quantitative trait loci for hypertension [63]. As described above, rostafuroxin reduces blood pressure in hypertensive MHS rats [53, 54] and humans [59] with adducin mutations.

α-Adducin polymorphisms have been described in human salt-sensitive hypertension as well. In an Italian study of 936 persons, including 137 hypertensive sibling pairs in whom linkage analysis was done using three DNA markers at different distances from the alpha-adducin locus (20–2,500 kb), and hypertensive patients, and normotensive controls, in whom the G460W polymorphism was studied, a significant association was seen between alpha-adducin and hypertension [64]. Interestingly, this relationship was not seen in a cohort of 375 Scottish patients [65] or 507 Japanese patients [66].

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 redistribution of salt and water to other body compartments occurs to offset this effect and the accompanying increase in blood pressure. *Osmotically active sodium* refers to the changes in total body water that occur with sodium intake. In contrast, *osmotically inactive sodium* describes sodium distribution that does not alter volume and that may protect against sodium-induced changes in blood pressure.

This concept of osmotically active and inactive sodium was studied in the Dahl salt-sensitive (SS) rat strain [67]. Compared to the Dahl salt-resistant strain and the Sprague-Dawley (SD) rat, SS rats had an expected increase in total body water, total body salt, and blood pressure when fed a high-salt diet. 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 (TBS) 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 appeared to contribute to the development of hypertension.

Titze et al. later studied the role of skin in SD rats as a compartment for osmotically inactive sodium [68]. Ovariectomized rats were compared to male and fertile female Sprague-Dawley rats, based on prior observation of altered 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. These investigators 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 [69]. The regulation of sodium in this compartment may be further connected to hormonal mechanisms within local macrophages [70] suggesting a complex interplay of mechanisms to regulate salt balance in this model of salt-sensitive hypertension.

Conclusions

Aberrant ion transport appears critical for the pathogenesis of hypertension. The research reviewed in this chapter reflects only a subset of the published data in this field. Changes in ion transport in hypertension also constitute an exciting area of potential study in children and adolescents with essential hypertension, many of whom are salt sensitive. The role of rostafuroxin remains to be established in the treatment of hypertension but establishes a new class of agent that may more directly target salt-sensitive essential hypertension without the complicating metabolic side effects of thiazides.

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Uric Acid in the Pathogenesis of Hypertension

5

Daniel I. Feig

Abstract

Over the last century, uric acid has been considered a possible risk factor for hypertension and cardiovascular disease. However, only in the last decade have animal models and clinical trials supported 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 the activation of renin-angiotensin-aldosterone system, followed by enhanced uric acid uptake into vascular smooth muscle cells leading to cellular proliferation and secondary arteriolosclerosis that impairs pressure natriuresis. This acute hypertension 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 serum uric acid can reduce blood pressure. While more research is clearly necessary, the available data suggest that uric acid may be causative in some cases of early onset hypertension.

Keywords

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

The History of Uric Acid and Hypertension

The possibility that uric acid may be a cause 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 vasculature of the heart and kidneys [1]. While he suggested several

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candidate molecules, he proposed uric acid as an important mediator and published the first sphygmograph tracings showing a patient with gout and increased systemic blood pressure [1]. A few years later Alexander Haig also linked uric acid with elevated blood pressure and wrote a textbook that suggested a diet to lower uric acid and control blood pressure in the general population [2]. 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 [3]. 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 [4]. In 1913, Desgrez reported the first animal model evidence supporting the link between uric acid and hypertension, noting that uric acid infusions increased blood pressure in a rabbit model [5]. 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 already linked with hypertension and cardiovascular diseases.

Interest in the possible link between hypertension and uric acid waxed and waned during much of the twentieth century. 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) [6]. The first was a lack of a plausible physiological mechanism and the second was that despite consistent correlation, the link between serum uric acid and cardiovascular disease was not always statistically independent of other factors such as hypertension, renal disease, and diabetes. In the 1980s, uric acid was removed from some of the common laboratory panels, markedly reducing the available epidemiologic data on uric acid both in otherwise 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 [7]. Thus, 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.

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 established a plausible mechanism that uric acid received greater attention (Table 5.1). Using a rat model of pharmacologically induced hyperuricemia, they found that increased serum uric acid results in hypertension within 2 weeks, with increases in SBP and DBP proportional to those of uric acid. The experimental hypertension can be ameliorated by uric acid lowering drugs (allopurinol or benziodarone). Early hypertension in this model is completely reversible with urate reduction, but prolonged hyperuricemia results in irreversible sodium-sensitive hypertension that becomes uric acid independent [8, 9]. 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 [8, 10–12], leading to a phenotype of excessive vasoconstriction that can be reversed by reduction of uric acid or by renin-angiotensin-aldosterone (RAAS) 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 [13–17] (see Fig. 5.1). If recapitulated in

Table 5.1 Animal model data that support a role for uric acid in hypertension

Uric acid effect	System	Specific observations	Reference
Causes hypertension in rats	Rats fed uricase inhibitor	Hyperuricemia resulted in hypertension within 2 weeks. SBP and DBP proportional to serum uric acid. Hypertension ameliorated by uric acid-lowering drugs (allopurinol or benziodarone). Prolonged hyperuricemia resulted in irreversible salt-sensitive hypertension	[8, 9]
Causes endothelial dysfunction in rats	Rats fed uricase inhibitor	Hyperuricemic rats had lower plasma nitrates than controls. Treatment with L-arginine corrected the hypertension and increased urinary nitrites. The mechanism likely resulted from stimulation of arginase and by direct reaction of NO to form aminouracil	[8, 10–12, 67]
Activates RAS in rats	Rats fed uricase inhibitor	Renal renin was 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	[9, 68]
Causes arteriolosclerosis in rats	Rats fed uricase inhibitor	Hyperuricemia induced renal microvascular injury resulting in renal ischemia, intrarenal inflammatory cell infiltration, intrarenal oxidative stress, and the development of hypertension	[16, 69–73]
Exacerbates progressive renal injury in rats	Rats fed uricase inhibitor	Hyperuricemic rats developed spontaneous renal disease, with progressive glomerulosclerosis and tubulointerstitial fibrosis. Hyperuricemia exacerbated glomerulosclerosis and GFR declined in 5/6 nephrectomy and cyclosporine nephrotoxicity models	[15]
Causes metabolic syndrome in rats	Rats fed uricase inhibitor	High fructose diet resulted in hyperuricemia, weight gain hyperinsulinemia, and hypertriglyceridemia within 4 weeks. This was mitigated by uric acid-lowing agents	[52]
Causes endothelial cell dysfunction in vitro	Primary endothelial cell culture	Uric acid inhibited NO production by HUVEC cells and decreased cell proliferation and migration. Mechanisms include induction of arginase, scavenging NO, and formation of aminouracil	[11, 12, 67, 74]
Causes vascular smooth muscle cells proliferation	Primary vascular smooth muscle cell culture	Uric acid entered 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)	[13, 17]
Impaired adipocyte function	Adipocyte tissue culture	Uric acid downregulated PPARγ and adiponectin	[11]

humans, this model implies that there may be a period of reversible hyperuricemic hypertension early in its development.

These mechanistic studies, as well as the recent epidemiologic data described below, have led to increased numbers of investigations and more research publications that address the link between uric acid and hypertension. Figure 5.2 shows the increase in publications graphically.

Epidemiology

Numerous longitudinal cardiovascular risk trials have evaluated the possible relationship between serum uric acid, hypertension, cardiovascular disease, and chronic kidney disease (see Tables 5.2, 5.3, and 5.4). As early as 1972, the Israeli Heart Trial, an evaluation of the medical data of young

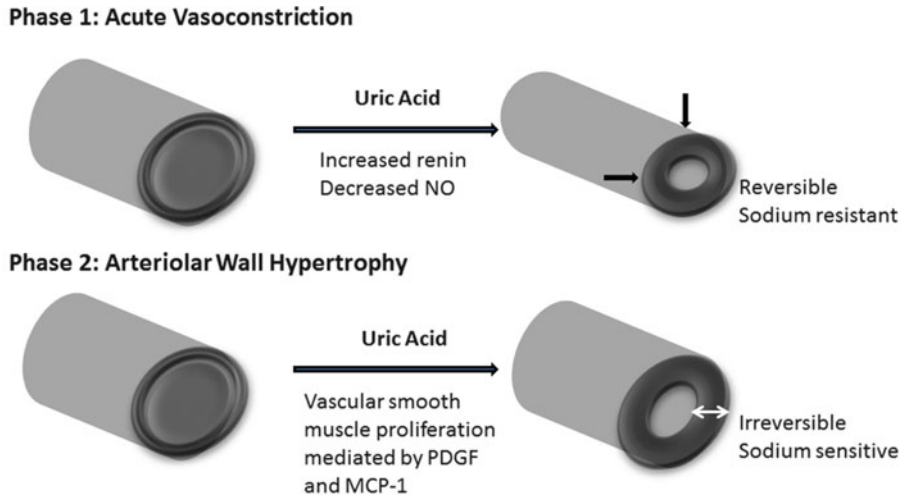

Fig. 5.1 Animal model data suggest that hyperuricemia leads to hypertension in a stepwise fashion. The effects of uric acid on the blood vessel are shown. The first phase is direct, uric acid-dependent activation of the renin-angiotensin-aldosterone system and downregulation of the nitric oxide production, 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 arteriolosclerosis. Uric acid uptake into vascular smooth muscle cells causing the activation and elaboration of PDGF and MCP-1. This results in the autocrine stimulation of vascular smooth muscle cell proliferation, vascular wall thickening, loss of vascular compliance, and a shift in pressure natriuresis. This process is not reversed by the late reduction of uric acid and causes permanent sodium-sensitive hypertension

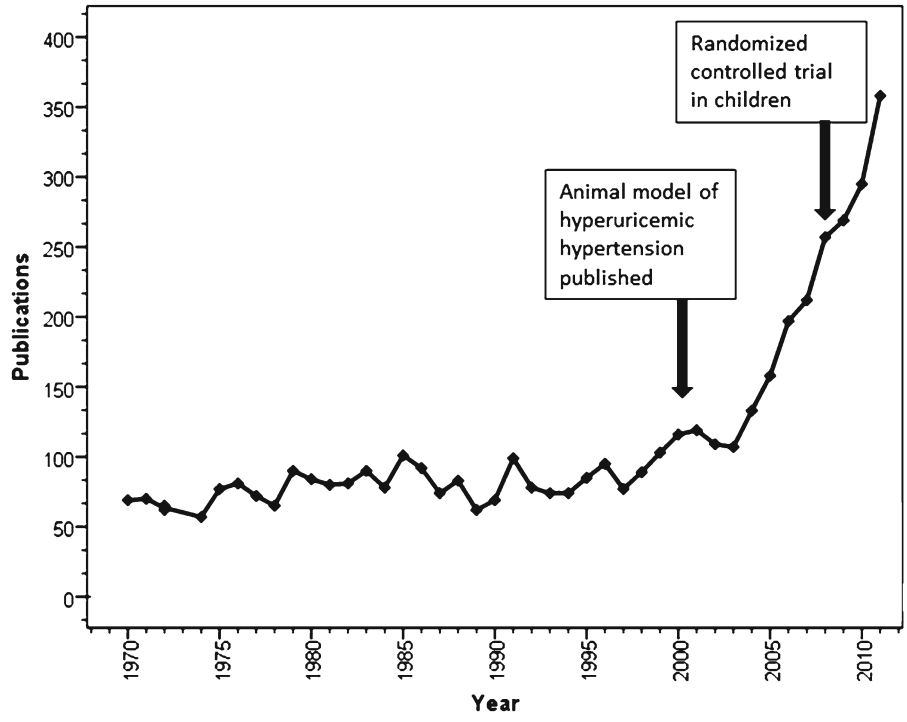

Fig. 5.2 Number of research articles published per year, 1970–2011, on the topic of the role of uric acid in hypertension. Articles were identified on PubMed using search terms uric acid, urate, hypertension, cardiovascular disease, fructose, sweetened beverages, xanthine oxidase inhibitors, allopurinol, uricosurics, and probenecid. Reviews were excluded and abstracts were reviewed for relevance

Table 5.2 Epidemiology of uric acid and hypertension and cardiovascular disease

Study	Population	Risk of hypertension	Reference
Israeli Heart (1972)	10,000 Israeli men aged 17–25 enrolled at military induction	Highest vs. lowest tertile of uric acid had twofold risk at 5 years	[18]
Fessel (1973)	224 white males in Western America, aged >35 years	Patients with baseline uric acid >7 mg/dL greater increase in SBP and increased risk of fatal and non-fatal CV events at 4 years	[75]
Gruskin (1985)	55 adolescents, racially mixed US population	76 % of patients with hypertension had Serum uric acid >7 mg/dL	[61]
Moscow Children's Study (1985)	145 Caucasian children in Moscow aged 8–17	Uric acid >8 mg/dL predicts severe hypertension in adulthood	[26]
Brand (1986)	4,286 men and women aged 35–50 in the Framingham cohort, cross-sectional data	Uric acid and SBP have a close linear correlation	[76]
Hungarian Children's (1990)	17,643 Hungarian children aged 6–19	Uric acid >6 mg/dL predicts development of hypertension in 5 years	[25]
Kaiser Permanente (1990)	2,062 adult men and women in the Kaiser Permanente Multiphasic Health Checkup cohort in Northern California	2-fold increased risk of systolic hypertension at 6 years	[77]
University of Utah (1991)	1,482 adult men and women in 98 Utah pedigrees	Twofold risk of hypertension at 7 years	[78]
NHANES (1993)	6,768 healthy children aged 6–17	Uric acid predicts adolescent hypertension at next follow-up visit	[27]
Olivetti Heart Study (1994)	619 adult males from Southern Italy	Twofold risk of hypertension at 12 years by end of follow-up	[79]
CARDIA study (1999)	5,115 black men and women aged 18–30	Increased risk of hypertension at 10-year follow-up	[19]
Osaka Health Survey (2001)	6,356 Japanese men aged 35–60	2-fold risk at 10-year follow-up	[24]
Hawaii-LA-Hiroshima Study (2001)	140 Japanese American males aged 40–69	3.5-fold risk at 15-year follow-up	[20]
Feig and Johnson (2003)	175 racially diverse children aged 6–18 in Texas	Uric acid >5.5 mg/dL predicts hypertension at time of presentation	[62]
Osaka Factory Study (2003)	433 non-obese Japanese men aged 18–40	Each 1.0 mg/dL associated with ↑27 mmHg SBP at 5 years	[21]
Osaka Health Survey (2003)	2,310 male office workers in Japan aged 35–59	1.6-fold risk at 6-year follow-up	[23]
Okinawa (2004)	4,489 Japanese men and women aged >30	1.7-fold risk at 13-year follow-up	[22]
Bogalusa Heart (2005)	577 black (58 %) and white (42 %) children enrolled at age followed until ages 18–35	Twofold ↑ risk for diastolic HTN at 11 years	[34]
Framingham (2005)	3,329 men and women in the Framingham cohort	1.6-fold at 4-year follow-up	[35]
Normative Aging Study (2006)	2,062 healthy men aged 40–60 at enrollment	1.5-fold at 21-year follow-up	[80]

(continued)

Table 5.2 (continued)

Study	Population	Risk of hypertension	Reference
ARIC (2006)	9,104 mixed race (black and white) men and women aged 45–64 years at enrollment	1.5-fold at 9-year follow-up	[81]
Beaver Dam Survey (2006)	2,520 white men (44 %) and women (56 %) aged 43–84 In Wisconsin	1.65-fold at 10-year follow-up	[82]
Health Professional Follow-up (2006)	750, mostly white men in Massachusetts	1.08-fold at 8-year follow-up	[83]
MRFIT (2007)	3,073 men aged 35–57 years	1.8-fold at 6-year follow-up	[84]
Nurses Health(2009)	1,496 women, racially diverse, aged 32–52	1.9-fold at 6-year follow-up	[85]
Qingdao Port Health (2009)	7,220 men (74 %) and women (26 %) in Qingdao, China mean age 37	1.39 for men, 1.85 for women at 4-year follow-up	[86]
Jones (2009)	141 children aged 7–18, 64 % male, 71 % black	2.1-fold risk in adolescence by ABPM	[87]
Leite (2010)	1,410 men and women in Milan, Italy, young cohort 42–59 years, older cohort 60–74	Increased risk in middle age, not elderly	[88]
Grayson (2010)	55,607 adults, meta-analysis of 18 prospective studies	1.41-fold risk each 1 mg/dL uric acid	[89]
Silverstein (2011)	108 racially diverse children aged 6–18 in Texas and Washington DC.	linear association between SBP and uric acid in children on renal replacement therapy	[41]
GOCADAN (2012)	1,078 Alaskan native Americans with CKD II-III	1.2-fold age-adjusted risk in patients in vs. lowest tertile of uric acid	[90]
Fadrowski (2012)	6,036 adolescents aged 11–17 evaluated in NHANES	Uric acid >5.5 mg/dL, 2.03-fold risk at next follow-up visit	[91]

armed services inductees, demonstrated that the highest tertile of uric acid was associated with doubling the risk of incident hypertension within 5 years [18]. The association appears to be robust across racial groups with similar findings in African Americans noted in the CARDIA trial [19] as well as several trials demonstrating the same association in Asians and Asian Americans [20–24]. Several studies in children and adolescents, particularly the Hungarian Children's Study [25], the Moscow Children's Study [26], and the National Health And Nutrition Examination Survey (NHANES) [27], in the 1980s and early 1990s, demonstrated a particularly strong association between uric acid and hypertension. Studies specifically of older and elderly patients have had more variable results [6, 28–30]. In particular, some of the studies found that the association between uric acid and cardiovascular (CV) risk did not retain significance in certain multiple regression models, particularly if the risk conferred by hypertension is controlled in the model [6, 31–33]. One explanation may be that the CV risk caused by uric acid functions through the development of hypertension; 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 serum uric acid and incident hypertension. Nakanishi et al. demonstrated a 1.6-fold increased risk of new hypertension over 6 years in young adult office workers with serum uric acid in the highest tertile [23]. In the Osaka Health Study, Tanaguichi et al.

Table 5.3 Epidemiology of uric acid and cardiovascular disease

Study	Population	CV Risk	Reference
Lehto (1998)	1,017 diabetics, mean age 58 years, followed for 7 years	OR 1.91, independent on MR	[92]
Liese (1999)	1,044 healthy adults, 50–60 years old, followed for 8 years	OR 1.7–2.8, independent on MR	[93]
Alderman (1999)	7,978 hypertensive adults, mean age 53 years, followed for 6 years	OR 1.5, independent on MR	[94]
Fang (2000)	5,926 healthy adults, mean age 48, followed for 16 years	OR 3.0, independent on MR	[95]
Franse (2000)	4,327 elderly adults, mean age 71, followed for 5 years	OR 1.5, independent on MR	[96]
Verdecchia (2000)	1,720 adults with hypertension, mean age 51 years, followed for 4 years	OR 1.9, independent on MR	[97]
Mazza (2001)	3,282 healthy adults, mean age 74, followed for 14 years	OR 1.6, independent on MR	[98]
Wang (2001)	1,873 Chinese adults, mean age 66 years, followed for 3 years	OR 1.34, independent on MR	[99]
Bickel (2002)	1,017 with coronary artery disease, mean age 62, followed for 2.2 years	OR 2.7, independent on MR	[100]
Weir (2003)	2,482 stroke patients, mean age 72, follow-up 2 years	OR 1.3, independent on MR	[101]
Niskanen (2004)	1,423 healthy Finnish adults, mean age 53 years, followed for 12 years	OR 4.8, independent on MR	[102]
Athyros (2004)	1,600 adults with hypertension and congestive heart failure, mean age 59, followed for 3 years	OR 3.0, independent on MR	[103]
Hakoda (2005)	10,615 atomic bomb survivors, mean age 49, followed for 25 years	OR 1.8, independent on MR	[104]
Suliman (2006)	294 adults with ESRD, mean age 53, followed for 3 years	OR 1.3, independent on MR	[105]
Bos (2006)	4,385 adults in Rotterdam study, above age 55 years, followed for 8.5 years	OR 1.7, independent on MR	[106]
Culleton (1999)	6,763 adult men, mean age 47, followed for 4 years, Framingham cohort	OR 4.1, not independent on MR	[6]
Moriarity (2000)	13,504 healthy adults, mean age 50, followed for 8 years	OR 3.0, not independent on MR	[31]
Sakata (2001)	8,172 healthy adults, mean age 49, followed for 14 years	OR 2.3, not independent on MR	[32]
Simon (2006)	2,763 women, mean age 66, followed for 4 years	OR 1.1, not independent on MR	[33]

demonstrated a twofold increased risk of new hypertension over 10 years associated with elevated uric acid [24]. Masuo et al. evaluated the linear association of serum uric acid and systolic blood pressure, finding an average increase of 27 mmHg per 1 mg/dL increase in serum uric acid among non-obese young men [21]. In an ethnically diverse population within the Bogalusa Heart Study, higher childhood and young adult serum uric acid levels were associated with incident hypertension and progressive increase in blood pressure even within the normal range [34]. A post hoc analysis from the Framingham Heart Study also suggested that a higher serum uric acid level is associated with increased risk of rising blood pressure [35]. 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 (Table 5.3);

Table 5.4 Epidemiology of uric acid and hypertension and chronic kidney disease

Study	Population	Major findings	Reference
Iseki (2001)	6,403, Okinawa General Health	Uric acid >8 mg/dL increase CKD risk threefold in men and tenfold in women	[107]
Siu (2006)	54 middle-aged men, nonrandomized treatment trial	CKD patients with mean uric acid of 9.75 mg/dL treated with 100–300 mg/dL allopurinol, possible slower progression	[37]
Chonchol (2007)	5,808, Cardiovascular Health Study	Uric acid strongly associated with prevalent but weakly with incident CKD	[108]
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	[38]
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	[109]
Sturm (2008)	227, Mild to Moderate Kidney Disease (MMKD) Study	Uric acid predicted progression of CKD only in unadjusted sample	[110]
Weiner (2008)	13,338, Atherosclerosis Risk in Communities (ARIC)	Each 1 mg/dL increase in uric acid increases 7–11 % risk of CKD	[111]
Borges (2009)	385 adult women	Elevated uric acid associated with 2.63-fold increased risk of CKD in hypertensive women	[112]
Chen, N (2009)	2596, Ruijin Hospital, China	Linear correlation between uric acid and degree of CKD	[113]
Chen, Y (2009)	5722, Taipei University Hospital	Uric acid associated with prevalent CKD in elderly	[114]
Hsu (2009)	177,570, United States Renal Data System (USRDS)	Higher uric acid quartile conferred 2.14-fold increased risk of ESRD over 25 years	[57]
Madero (2009)	840, Instituto Nacional de Cariologia, Mexico	Patients with CKD 3–4 and uric acid correlates with death but not to ESRD	[115]
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	[116]
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	[117]
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	[118]
Ejaz (2012)	100 consecutive adult cardiac surgery patients	In comparison to lowest tertile of uric acid, highest had fivefold risk of AKI during hospital stay	[39]
Ejaz (2012)	26 hyperuricemic cardiac surgery patients randomized to pre-op Rasburicase or placebo	Uric acid reduction results in reduction of post op urinary neutrophil gelatinase associated lipocalin (uNGAL) but no statistically significant difference in serum creatinine	[40]

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 [6, 31, 32, 36], suggesting some or all of the impact of uric acid on cardiovascular risk may be mediated through its effects on hypertension.

The association between uric acid and CKD is more difficult to assess. While hypertension itself

and the vasculopathic mechanism proposed to explain uric acid-mediated hypertension (Fig. 5.1) would be expected to contribute to renal ischemia and glomerular hypoperfusion, decreased glomerular filtration rate itself would increase serum uric acid, confounding mechanistic conclusions. Several epidemiologic trials have found an association between elevated serum uric acid and renal functional decline (see Table 5.4), though a similar number have the association lacked statistical significance. To date only two published clinical trials have shown reduced progression of renal injury in association with uric acid lowering therapy. Siu and colleagues treated 53 adult men with mean serum uric acid of 9.5 mg/dL and found a trend toward slower functional decline than historical controls [37]. Kanbay and colleagues randomized 59 young adults CKD to treatment with allopurinol or placebo; those in the active treatment group had a statistically significant increase in GFR in comparison to controls [38]. Uric acid has also been implicated in the potentiation of acute kidney injury (AKI). Animal models indicate that elevated uric acid causes synergistic damage in cyclosporine and the 5th/6th nephrectomy models of renal injury. In adults undergoing cardiac bypass surgery, patients in the highest tertile of serum uric acid are 5 times more likely to develop AKI [39]. 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 resulted in a reduction in levels of the renal injury biomarker NGAL (neutrophil gelatinase-associated lipocalin), though no short-term difference in serum creatinine was seen [40].

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 result from decreased renal function and in general, children with CKD and ESRD have higher serum uric acid levels than normal children [41]. Genetic polymorphisms in anion transporters such as the uric acid anion transporter 1 (URAT-1) [42] and the SLC2A9 that encodes for GLUT9, an anion transporter with affinity for uric acid [43, 44], 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 serum uric acid [45]. Diets rich in fatty meats, seafood and alcohol increase serum uric acid [46, 47], and obesity confers a threefold increased risk of hyperuricemia [48]. 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 [49], 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 serum uric acid [50].

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 [51, 52]. Fructose raises uric acid rapidly via activation of the fructokinase pathway in hepatocytes [53]. Fructokinase consumes ATP leading to an increased load of intracellular purines requiring metabolism and disposal through xanthine oxidase-mediated metabolism ending in uric acid [53, 54] (see Fig. 5.3). The administration of large quantities of fructose to rats, 60 % of their caloric intake, results in hyperuricemia, elevated blood pressure, and the development of preglomerular arteriolopathy [55]. Furthermore, lowering uric acid prevents these changes, despite ongoing fructose consumption [52]. 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, genetically deficient in uricase, may require less fructose consumption to result in hyperuricemia.

Human studies show that fructose loading leads to increased serum uric acid levels acutely and that chronic increases in fructose consumption lead to chronically increased serum uric acid and

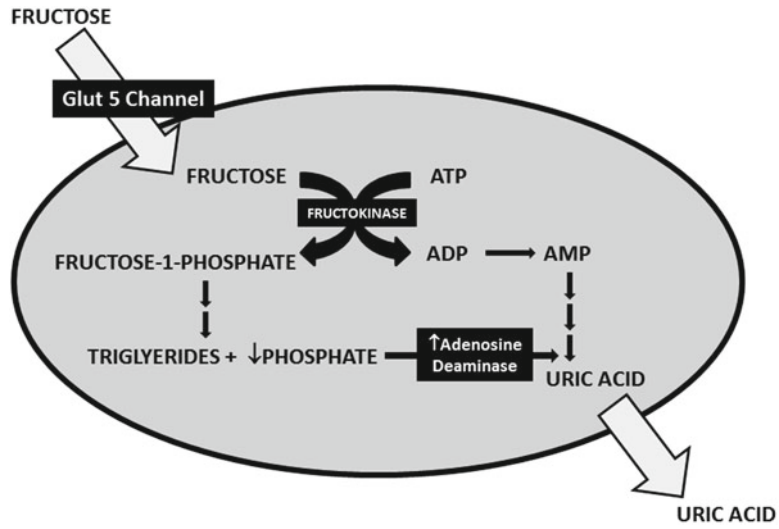

Fig. 5.3 The effect of cellular fructose metabolism on serum uric acid: Soluble fructose is taken up into multiple cell types, particularly hepatic cells and adipocytes, via the GLUT5 transporter. Fructose is then phosphorylated by fructokinase. Unlike glucokinase, fructokinase does not respond to feedback 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 54

increases in blood pressure [56]. With the nearly universal exposure to sweetened foods and beverages among children, it is very likely that much of the hyperuricemia, especially that associated with obesity, is dietary rather than genetic in origin [57]. Consistent with this hypothesis, epidemiological studies have shown a relationship of fructose with serum uric acid in most but not all studies [58]. One reason some studies may be negative could reflect the action of fructose, which tends to increase uric acid primarily in the postprandial setting. Some studies measured only fasting uric acid levels, so it is possible that an elevation in mean 24-h uric acid excretion would be missed.

Jalal and colleagues used the National Health and Nutrition Examination Survey (NHANES 2000–2003), which was a survey of healthy adults in the United States in which direct blood pressure measurement as well as dietary intake of fructose as determined by dietary questionnaire were available. The major finding was that there was a strong independent relationship of fructose intake with elevated systolic blood pressure [58]. Interestingly, the relationship was independent of fasting serum uric acid. In a different study Nguyen and colleagues also found an independent relationship of sugary soft drinks with hypertension in adolescents [57]. Perez-Pozo et al. administered 200 g of fructose per day to healthy overweight males with or without allopurinol over a 2-week period [59] and observed an increase in serum uric acid in association with a significant increase in daytime systolic and both 24-h and daytime diastolic blood pressures. Allopurinol reduced the serum uric acid and blocked the increase in blood pressure. While the dose of fructose was very high in the Perez-Pozo study, 25 % of the NHANES cohort actually reported having consumed similar quantities [58].

Pediatric Clinical Trials

A close association has been reported between elevated serum 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 [60]. 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 [25]. These two studies do not separate the hypertensive children by underlying diagnosis, i.e., essential hypertension versus that caused by renal, cardiac, or endocrinologic causes independent of uric acid, so the relationship between serum uric and hypertension may be attenuated somewhat. In a small study, Gruskin [61] 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 serum 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 serum uric acid level (±SD) in controls was 3.6 ± 0.8 mg/dL, similar to that in children with white coat hypertension – 3.6 ± 0.7 mg/dL. It was slightly higher in children with secondary hypertension (4.3 ± 1.4 mg/dL, $p = 0.008$) but significantly elevated in children with primary hypertension (6.7 ± 1.3 mg/dL, $p = 0.000004$) [62]. There was a tight, linear correlation between the serum 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 serum uric acid was associated with an average increase of 14 mmHg in systolic blood pressure and 7 mmHg in diastolic blood pressure [62]. Among patients referred for evaluation of hypertension, a serum uric acid >5.5 mg/dL had an 89 % positive predictive value for essential hypertension, while a serum uric acid <5.0 had a negative predictive value for essential hypertension of 96 % [62].

Results from small pilot studies in children suggest that uric acid may directly contribute to the onset of hypertension in some people. In one study five children, 14–17 years of age, with newly diagnosed and as yet untreated essential hypertension were treated for 1 month with allopurinol as a 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 one month [63]. 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 serum uric acid levels <5.5 mg/dL on treatment, had normal blood pressure, as compared to 3 % of children on placebo [64].

Such preliminary clinic trial data raise two important questions. 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 [65]. 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 to date demonstrate that the mechanism of blood pressure lowering is definitely uric acid reduction and the effects can be demonstrated in children with prehypertension, not just stage 1 hypertension.

While these observations require confirmation in larger and more general populations, if serum

uric acid is indeed directly causing renal arteriolopathy, 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.

Conclusions

The combination of epidemiologic, animal model and clinical trial support a causative role for uric acid in some patients with elevated blood pressure. The controversy over its role 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 RAAS, 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 would explain the greater magnitude of effect seen in younger patients or at least the attenuation of affect in the elderly. Second, it may represent a unique opportunity in newly diagnosed hyperuricemic hypertension, in which metabolic control may delay or prevent irreversible vasculopathy and permanent future hypertension.

The best approach to 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 hypertensions with current conventional approaches that bespeak the need for novel therapeutics. The link between fructose intake and serum uric acid may also hold important promise; however, while fructose loading clearly leads to increased serum uric acid and increased blood pressure in clinical trials, the efficacy of fructose reduction has not been proven. A post hoc evaluation for the PRIMIER trial, a large trial of the efficacy of non-pharmacologic 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 [66]; however, additional research is needed to confirm its efficacy.

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Monogenic and Polygenic Contributions to Hypertension

6

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 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.

Keywords

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

Introduction

More than 12 years have elapsed since the publications in February 2001 that provided the first maps of the human genome [1, 2]. While genes involved in a number of rare, monogenic forms of hypertension have been identified, the genetics of primary hypertension has eluded delineation, 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 aspects of hypertension. We also discuss the current clinical implications of genetic studies and information in our approach to hypertension [3].

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"] [4–6]. In this approach, large kindreds with many

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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 centimorgan [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 4.5×10^{-5} [4]]. Once linkage is identified, 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.

A number of monogenic forms of hypertension have been identified to date. A number are due to gain-of-function mutations [7–9], most of which involve the renal handling of salt 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. 6.1 [10].

Gain-of-function mutations in transporters in the distal renal tubules result in hypertension via salt and water retention [11]. (While mutations and polymorphisms in the genes of various

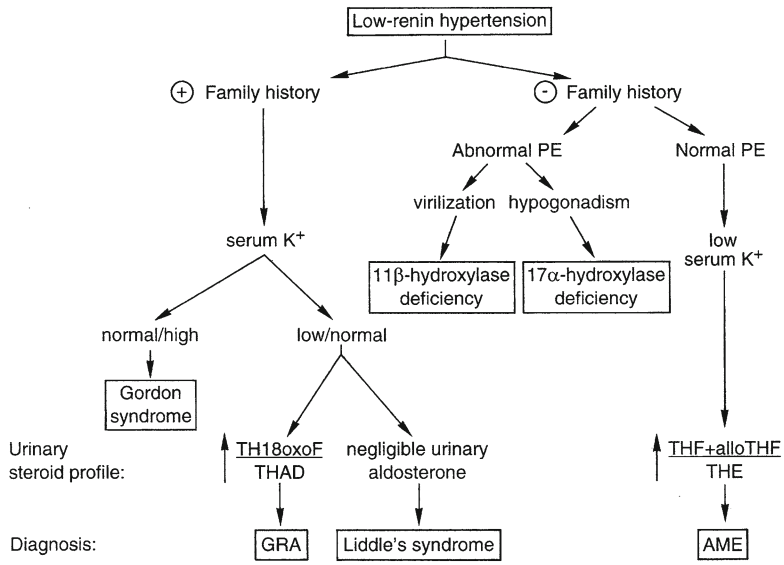

Fig. 6.1 Evaluation of patients with hypertension and low plasma renin. Such disorders are either autosomal dominant, generally with a positive family history, or autosomal recessive, generally with a negative family history. Children with glucocorticoid-responsive aldosteronism (GRA), Liddle syndrome, 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. K+, potassium, TH18oxoF/THAD ratio, ratio of urinary 18-oxotetrahydrocortisol (TH18oxoF) to urinary tetrahydroaldosterone (THAD), which has a normal of 0–0.4, and GRA patients >1. THF plus alloTHF/THE ratio of the combined urinary tetrahydrocortisol (THF) and allotetrahydrocortisol (alloTHF) to urinary tetrahydrocortisone (THE), which has a normal of <1.3, while AME patients are 5–10-fold higher (From Yiu VW, Dluhy RG, Lifton RP, Guay-Woodford LM. Low peripheral plasma renin activity as a critical marker in pediatric hypertension. Pediatr Nephrol. 1997;11: 343–6, with permission)

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 electrolyte transport, focusing attention on the role of the kidney in hypertension (Table 6.1) [7]. Additionally, some mutations in proto-oncogenes and genes that involve response to hypoxia have been linked to chromaffin tumors (Table 6.2) [12]. Information about the most common forms of monogenic hypertension [13] follows.

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 [14–18]. GRA has been recognized since the 1960s, when Sutherland et al. [19] and New et al. [20] reported patients with severe hypertension accompanied by suppressed 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 adrenocorticotropic 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 as the main controller of aldosterone secretion [21, 22]. 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 [23–25], 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 [26]. 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 [27–29]. Dluhy et al. [27] 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 [27].

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 [7, 8, 21].

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 adenoma producing aldosterone or both [30–33]. It has been estimated to be fivefold more common than GRA [33]. Dexamethasone fails to suppress the hypertension. To date, no mutation has been identified, though linkage studies have identified a five megabase locus on chromosome 7p22. The Stowasser group [33] has examined a number of candidate genes within 7p22, many of which involve cell growth, but has still not yet definitively identified the gene responsible.

Table 6.1 Adapted and expanded from [147]

Signs and sx	Hormonal findings	Source	Genetics	Comment
Steroidogenic enzyme defects				
Steroid 11β- hydroxylase deficiency	⇓ PRA and aldo; high serum androgens/ urine 17 ketosteroids; elevated DOC and 11-deoxycortisol	Adrenal: zona fasciculata	CYP11B1 mutation [encodes cytochrome P_{450}11β/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 11α-hydroxylase/ 17,20-lyase deficiency	⇓ PRA and aldo; low serum/urinary 17-hydroxysteroids; decreased cortisol	Adrenal: zona fasciculata; Gonadal: interstitial cells [Leydig in testis; theca in ovary]	CYP17 mutation [encodes cytochrome P_{450}C17] impairs cortisol and sex steroid production	CAH with male pseudoher-maphroditism; female external genital phenotype in males; primary amenorrhea in females
	⇑ Corticosterone [B] and DOC in plasma; serum androgens and estrogens very low; serum gonadotropins very high			
Hyperaldosteronism				
Primary aldosteronism	⇓ 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 aldo-producing adenoma; muscle weakness and low K+ 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; ⇑ 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 mineralalocorti-coid 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. 11βOHSD or slow clearance by 5 α/β reduction to allo dihydro-F	Type 2 11βOHSD mutations	Cardiac conduction changes; LVH, vessel remodeling; some calcium abnormalities; nephrocalcinosis; rickets

Nonsteroidal defects				
Liddle syndrome	Low plasma renin, low or normal K+; negligible urinary aldosterone	Not a disorder of steroidogenesis, but of transport	Autosomal dominant Abnormality in epithelial sodium transporter, EnaC, in which channel is constitutively active	Responds to triamterene
Pseudohypoaldosteronism II – Gordon syndrome	Low plasma renin, normal or elevated K+	Not a disorder of steroidogenesis, but of transport	Autosomal dominant Abnormality in WNK1 or WNK4	Responds to thiazides
Hypertension exacerbated by pregnancy		Missense mutation of the mineralocorticoid receptor converts antagonists (such as progesterone) to agonists	NR3C2	
Mutations in peroxisome-activated receptor gamma		Loss of function mutation results in insulin resistance and hypertension	PPARG	

Table 6.2 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 angiomata, 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 RG. Pheochromocytoma: the death of an axiom. N Engl J Med. 2002;346:1486–8
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

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 [33–37].

Apparent Mineralocorticoid Excess [AME] [OMIM # 218030]

Low-renin hypertension, often severe and accompanied by hypokalemia and metabolic alkalosis [38], is the hallmark of apparent mineralocorticoid excess [AME], first described in 1977 by New et al. [39, 40]. Spironolactone is often effective initially, but patients often become refractory to this drug. In AME, 11β-hydroxysteroid dehydrogenase (11β-HSD) is absent, resulting in hypertension in which cortisol acts as if it were a potent mineralocorticoid. The microsomal enzyme, 11β-hydroxysteroid dehydrogenase, interconverts active 11-hydroxyglucocorticoids to inactive ketometabolites. Cortisol, as well as aldosterone, has an affinity for the mineralocorticoid receptor. Normally, 11β-HSD is protective, preventing 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 [39, 40], while 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 very low. Affected children are at high risk for cardiovascular complications, and some develop nephrocalcinosis and renal failure [41]; 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 and makes 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 [42, 43], a coactivator defect with resistance to multiple steroids [44], and hypertension without the characteristic findings of AME in a heterozygous father and homozygous daughter who have mutations in 11 β HSD2 [45]. Coeli et al. reported a Brazilian child with a homozygous missense mutation p.R186C in the HSD11B2 gene [46].

The hypertension in AME appears renally mediated, but recent evidence suggests that ultimately, the disorder changes from one with increased sodium resorption to a vascular form of hypertension [47].

Mineralocorticoid Receptor Gain-of-Function Mutation

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 renin and aldosterone levels, as well as mild hypokalemia [48]. 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)

Affected persons have refractory hypertension, and women with this mutation have severely elevated BP during pregnancy [49, 50]. Early death due to heart failure occurred in the index family [48].

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 in this mutation: these include RU 486, 5-pregnane-20-one, and 4,9-androstadiene-3,17-dione [51].

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. 25.

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 [52–54]. 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] 11β-hydroxylase >3β-hydroxysteroid dehydrogenase>17α-hydroxylase and cholesterol desmolase. Patients with the 11β-hydroxylase and 3β-hydroxysteroid dehydrogenase defects have a tendency to retain salt, becoming hypertensive. It is also important to remember that any person with CAH may develop hypertension owing to overzealous replacement therapy.

Steroid 11β-Hydroxylase Deficiency

The mineralocorticoid excess in 11β-hydroxylase deficiency [52–58], 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 11β-hydroxylase deficiency and most often is discovered in later childhood or adolescence, often with an inconsistent correlation to the biochemical profile [52–58]. Hypokalemia is variable, but total body potassium may be markedly depleted in the face of normal serum or plasma potassium. Renin is generally decreased, but aldosterone is increased.

Therapy of 11β-hydroxylase deficiency should focus on normalizing steroids. Administered glucocorticoids should normalize cortisol and reduce ACTH secretion and levels to normal, thus stopping over secretion of deoxycorticosterone (DOC). Hypertension generally resolves

with such therapy [53]. When hypertension is severe, antihypertensive therapy should be used instituted until the BP is controlled; such therapy can be tapered later.

Additional mutations can cause this syndrome. For example, a patient with 11β-hydroxylation inhibition for 17α-hydroxylated steroids but with intact 17-deoxysteroid hydroxylation has been reported [58]. Multiple mutations affecting the CYP11B1 gene have been described; these include frameshifts, point mutations, extra triplet repeats, and stop mutations [38, 59–62].

Steroid 17α-Hydroxylase Deficiency

Abnormalities in 17α-hydroxylase affect both the adrenals and gonads, since a dysfunctional 17α-hydroxylase enzyme results in decreased synthesis of both cortisol and sex steroids [63–66]. 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 [65]. An inguinal hernia is another mode of presentation. Hypertension and hypokalemia are characteristic, owing to impressive overproduction of corticosterone [compound B].

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.

Mutations in Renal Transporters Causing Low-Renin Hypertension

Pseudohypoaldosteronism Type II: Gordon Syndrome [OMIM#145260]

Pseudohypoaldosteronism type II, Gordon syndrome, or familial hyperkalemia (OMIM #145260), an autosomal dominant form of hypertension associated with hyperkalemia, acidemia, and increased salt reabsorption by the kidney, is caused by mutations in the WNK1 and WNK 4 kinase family [67–71]. Though the physiology and response to diuretics suggested a defect in renal ion transport in the presence of normal glomerular filtration rate, the genetics have only recently been delineated.

Affected persons have low-renin hypertension and improve with thiazide diuretics or with triamterene [71]. Aldosterone receptor antagonists do not correct the observed abnormalities.

PHAII genes have been mapped to chromosomes 17, 1, and 12 [67, 68]. 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. While WNK 1 is widely expressed, WNK4 is expressed primarily 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 by as yet unknown means.

Liddle Syndrome [OMIM # 177200]

In 1963, Liddle [72] 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 [73]. A major abnormality in renal salt handling seemed likely when a patient with Liddle syndrome underwent a renal transplant and hypertension and hypokalemia resolved posttransplant [74].

While the clinical picture of Liddle syndrome is one of aldosterone excess, aldosterone levels as well as renin levels are very low [10]. 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. Mutations in the beta and gamma subunits of the ENaC have been identified [both lie on chromosome 16] [75, 76]. 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 [77].

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 6.2 [12, 78–83]. A number of paraganglioma and pheochromocytoma susceptibility genes inherited in an autosomal dominant pattern appear to convey a propensity toward developing such tumors [12]. Both glomus tumors and pheochromocytomas derive from neural crest tissues, and the genes identified in one type of tumor may appear in the other [84]. 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] [85]. 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*).

The genes involved in some of these tumors appear to encode proteins with a common link involving tissue oxygen metabolism [86–88]. 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_2 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.

Hypertension with Brachydactyly [OMIM #112410]

Hypertension with brachydactyly, also called brachydactyly, type E, with short stature and hypertension (Bilginturan syndrome), was first described in 1973in a Turkish kindred [89]. 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 to p11.2 [90, 91].

Patients with this form of hypertension have normal sympathetic nervous system and renin-angiotensin system 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 [92]. Another family, in Japan, also had similar findings, and a deletion in 12p was reported in that family [93].

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 [94]). 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.

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 human peroxisome proliferator-activated receptor gamma (PPARγ), a transcription factor [95].

PPARγ is important in the differentiation of adipocytes (reviewed in Meirhaeghe and Amouyel [95]). Mutations in PPARγ have been linked to a group of symptoms, including hypertension. Only eight persons have been described to date and have point mutations that are heterozygous (V290M, R425C, P467L, and F388L) [95–99]. The affected patients have had marked insulin resistance, then develop type 2 diabetes, and have dyslipidemia, as well as hypertension. The finding of these patients has been taken widely as a demonstration of the importance of PPARG in metabolic syndrome and in blood pressure control.

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 [100].

When to Suspect Monogenic Hypertension

Table 6.3 lists those situations in which the astute clinician should consider monogenic hypertension [8]. 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 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.

Table 6.3 When to suspect a hypertensive genetic disorder

Patient is an at risk member of a kindred with a known monogenic hypertensive disorder (e.g., multiple endocrine neoplasia, syndromes)
Patient is a hypertensive child with hypokalemia whose first-degree relatives have hypokalemia and/or hypertension
Patient with juvenile onset of hypertension, particularly if plasma renin is suppressed
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 [8]

Non-Mendelian, Polygenic Hypertension

The genetic contribution to a prevalent condition such as essential [primary] 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:

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. 8). In the 1980s, it was estimated that 5–10 genes control BP [101]. In 2000, Rapp summarized available research and estimated that 24 chromosomal regions in 19 chromosomes were associated with hypertension in various rat strains [102]. A recent review by Delles et al. [103] 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 [104].

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 [105].

Genetic manipulation in mice has been successful in exploring contributions of various candidate genes (reviewed in [106]), most notably those of the RAAS through two approaches, overexpression of a given gene [with "transgenic" animals [102]] and deleting gene function [with "knockouts"]. An additional approach is to use gene targeting in embryonic stem [ES] cell cultures [107–109].

Inbred strains rather than transgenic or knockouts have led to important findings [109–112]. A number of studies, notably those of Jacob et al. [109] and Hilbert et al. [110], 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 nearly 20 years ago, a large number of clinical studies have suggested a link between ACE polymorphisms in humans and hypertension. See a recent commentary on the value of studies in the rat model [103, 111].

Human Hypertension

A variety of studies have pointed to a link between human hypertension and genes of the RAAS (summarized in references [112, 113]). 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 do not have 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 [114–129].

While linkage analysis may constitute an initial step (3–6), 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. 6.2). 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 (3–6). 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, 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 1×10^6 base pairs [121, 122].

Genome-wide screens of the human genome aiming to discover hypertension genes have suggested many loci of interest [123, 124]. 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 [123]. Using genomic scan data from four partner networks the US Family Blood Pressure Program (FBPP) [124] 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 [120] and Finnish twins [115], as well as a discordant

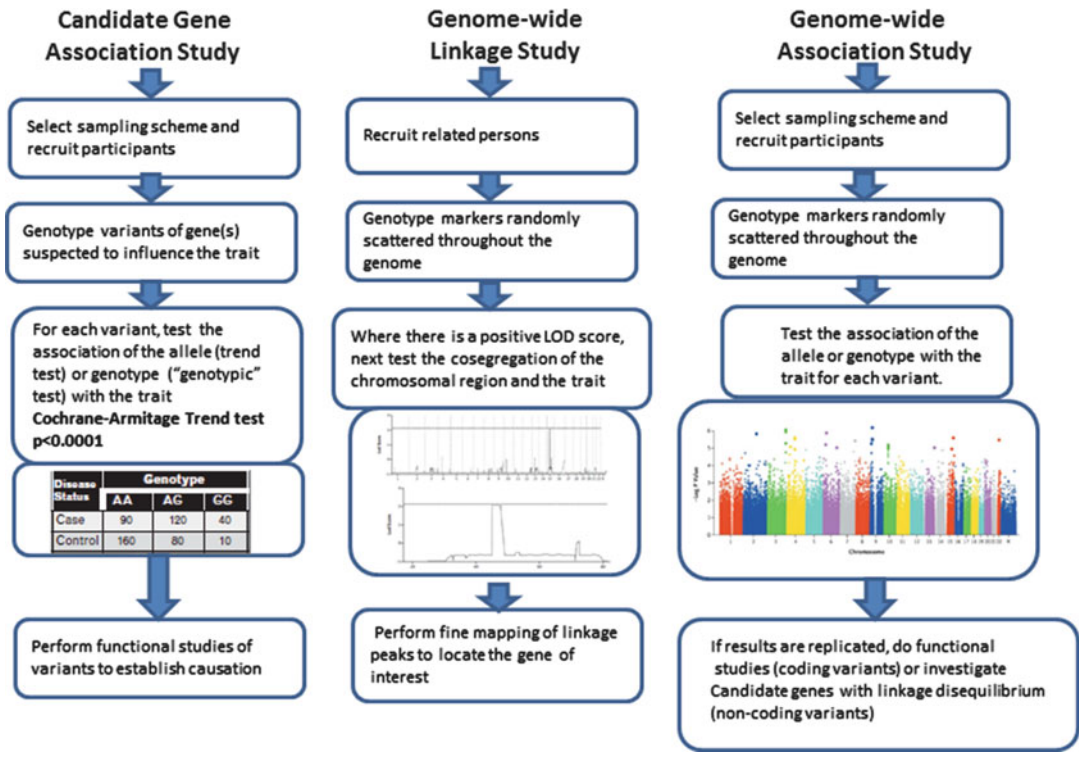

Fig. 6.2 Study designs used to dissect the genetic architecture of common complex traits. This figure shows the flow of studies that utilize candidate gene approaches, genome-wide linkage studies and genome-wide association studies (After Simino J, Rao DC, Freedman BI. Novel findings and future directions on the genetics of hypertension. Curr Opin Nephrol Hypertens. 2012;21(5):500–7, with permission. Insets for genome-wide linkage and genome-wide association studies are from Graphic Arts, the New England Journal of Medicine, with permission)

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 **BRI**tish **G**enetics of **H**yper**T**ension] and performed a 10 cM genome-wide scan [125]. 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 [125]. One of these loci was the same as that found in the Chinese and Finnish studies [125].

Within the last few years, there have been further genome-wide association studies (GWAS) concerning hypertension reported [130, 131]. In 2007 Levy et al. used an Affymetrix 100 k chip platform and performed a GWAS with the Framingham cohort, yet the initial analysis did not find significance for any single gene [132]. Using the Wellcome Trust Case Control Consortium [WTCCC] and an Affymetrix 500 k chip, another GWAS was reported in 2007, and it, too, did not reach genome-wide significance for any gene [133]. 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, Ca++-transporting, plasma membrane 1 (*ATP2B*) gene [134]. 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 2.5 million 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) [135]. Further, the so-called CHARGE consortium [136] looked at 29,136 participants and studied 2.5 million genotyped or imputed SNPs; they reported significant associations with hypertension for 10 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 [135]. These included the *ATP2B* gene, as well as *CYP17A1* (steroid 17-alphamonooxygenase), *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) [135].

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. If the full sequence of the candidate gene is known, then it is relatively easier to go forward.

In the Caulfield study [125], 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, 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. [128] 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 [117]. In a GWAS in African Americans, Adeyemo et al. [137] 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 [3–5, 118, 120]. 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 [118]. 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.

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. 6.2 and in recent reviews [138–144], would still indicate that the concept of a complex set of interactions leads to most cases of hypertension.

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 [139]. 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 [145, 146]. 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.

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.

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Perinatal Programming and Blood Pressure

7

Mahmoud Kallash, Julie R. Ingelfinger, and V. Matti Vehasakari

Abstract

Adverse intrauterine and perinatal events may have profound effects on the fetus and neonate. This chapter discusses both epidemiologic data and experimental models that elucidate those factors involved in perinatal programming and developmental origins of adult disease. Persons who have been born after exposure to an adverse intrauterine environment may be at higher risk of future diseases than those born after uneventful gestation. This phenomenon has been called "perinatal programming," a term suggesting the importance of the milieu during organogenesis to future events. The mechanisms by which perinatal programming occurs are multiple, involving subtle changes in development, changes in expression of various proteins, and, likely, epigenetic changes. Infants who are small for gestational age or are premature appear to be at high risk to be subject to the effects of programming. Whether such people should be considered as having an "extra" risk factor for hypertension and cardiovascular disease, as well as for metabolic syndrome and other conditions, is discussed in this chapter.

Keywords

Developmental origins of health and disease • Perinatal programming • Nephron endowment

Introduction

In the 1980s, British epidemiologist David Barker mined national records kept since the early part of the century to examine the relation between maternal health during pregnancy and cardiovascular disease of their offspring in later life, specifically non-hemorrhagic stroke [1]. A few previous publications had noted a statistical

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association between birth weight and hypertension in later life [2–4], and Barker subsequently formulated the hypothesis that prenatal and perinatal environment can impact later-life phenotype [1, 5, 6]. From his observations on stroke victims, who died at ages 55–74 years, he postulated that hypertension may be the link between low birth weight and later-life cardiovascular disease [1]. Initially called the "Barker hypothesis," the concept has since been variously called "prenatal programming," "perinatal programming," "developmental origins of health and disease," abbreviated as DOHaD, "developmental programming," or "developmental plasticity." As the latter terms imply, the concept has expanded to explain phenotypic characteristics other than diseases induced or caused by prenatal and early-life events. During the past two decades, the phenomenon of developmental programming has been a focus of intense study, but many of its aspects remain highly controversial and lack consensus, in part, because unraveling the underlying physiological mechanisms has proven elusive.

Of later-life disorders, hypertension has received the most attention in this field, and the bulk of the evidence supports the concept that the in utero environment can modify adult blood pressure patterns. It is important to note, as discussed below, that low birth weight may only be a marker of intrauterine stressors and may not have a causal role in the subsequent development of hypertension. There is also considerable evidence to suggest that the susceptible period extends to postnatal factors in early life.

Epidemiology of Low Birth Weight and Subsequent Hypertension

Geography, Ethnicity, and Gender

Most epidemiologic and other human studies about developmental programming have focused on the association of birth weight with subsequent events. Barker's early reports [1, 5, 6] took advantage of records available in a relatively limited geographic area (England and Wales). However, the association of LBW with hypertension has now been described in cohorts from numerous countries in Northern and Southern Europe [7, 8] [Finland, Norway, Sweden], North America [9–12], Central [13] and South America [13, 14], the Caribbean [15], Asia [16, 17], and Australia–New Zealand [18, 19]. The findings have largely been similar in all ethnic groups studied, including the indigenous peoples of Australia [18, 20]. The possible exception are persons of African ancestry in whom the findings have been ambiguous [13, 21, 22] or even the opposite, with LBW subjects having lower BP [23, 24]. Interestingly, a recent paper reported that Colorado residents of Mexican heritage appeared to be partially protected from the adverse effect of low birth weight [25].

Most reports have compared persons who had a low birth weight, often defined as <2,500 g, to those with "normal" birth weight. Very low birth weight (<1,500 g) persons may be at an even higher risk for later hypertension [26–29], and the risk may be inversely correlated to immaturity at birth [30].

Most studies in people report no gender difference in the association between birth weight and later hypertension [7, 9, 10], with some exceptions. While female subjects were more affected in a twin study published by Loos et al. [31], other reports have shown a predominant effect in males [32].

Studies in identical twins have been employed to control for potential confounding genetic and other factors common to both twin pairs. Several studies have concluded that even between twins, the twin with the lower birth weight is likely to have higher blood pressure in adult life [31–33], suggesting an effect within the fetoplacental unit, rather than from maternal factors shared by both twins. Not all studies agree. For instance, a Belgian long-term cohort study of 418 twin pairs reported no correlation between intrapair birth weight and blood pressure in young adulthood, although an effect of birth weight was observed between pairs [31]. The fact that perinatal programming of hypertension can be induced in both inbred and outbred animal species indicates that the in utero environment may confer an effect independently of the inherited genome [33].

A few epidemiologic studies have disputed the relationship between birth weight and

hypertension [34]. For example, Seidman et al. [35] found no association of BW and later blood pressure in a cohort of >30,000 17-year-old men and women. Skepticism about the concept of prenatal programming has centered on the difficulty in controlling for all confounding variables in epidemiologic studies [36–38]. It has been noted that low birth weight is frequently associated with many other factors known to be associated with hypertension, such as maternal size, socioeconomic status, educational level, and geographic region in which the mother lives. These concerns were recently addressed in a large US longitudinal study of 39–56-year-olds [39]. The study demonstrated that while socioeconomic factors during early life predicted adult hypertension, there were significant independent contributions by birth weight, even between siblings [39]. Taking the data together, the link between low birth weight and later-life hypertension seems well established. Negative results may be explained by studies with small subject numbers and other confounding risk factors, and the young age of study subjects who have not yet become hypertensive.

Intrauterine Growth Restriction Versus Prematurity

Most large cohort studies in adults were unable to distinguish between low birth weight resulting from intrauterine growth restriction (IUGR) or from premature birth and, therefore, do not clearly indicate whether premature babies without IUGR (BW appropriate for gestational age) are at an increased risk for later hypertension. The strength of the evidence now suggests that prematurity by itself is a risk factor, causing organ and metabolic pathology similar to those seen in IUGR, including later-life hypertension [28, 40–43]. Therefore, it is possible that early postnatal stress has effects analogous to prenatal stress on a very immature organism. Some studies have suggested that prematurity may be a stronger independent predictor of subsequent hypertension than LBW [43]. This is an important point because in developed countries, prematurity is a much more common cause of LBW than IUGR.

Body Proportion and Postnatal Growth

It is possible that the postnatal catch-up growth that follows IUGR may have later effects on BP. Several studies have suggested that IUGR places the offspring on a trajectory to increased postnatal weight gain, which may be an additional factor leading to a programmed increase in BP. The reported sensitive time periods for detrimental weight gain have varied from 1 to 13 years of postnatal age [23, 44–48].

An additional point is that a "thin" body habitus (low ponderal index) at birth may be independently associated with later increase in BP, which may be independent of BW but amplified by large postnatal weight gains [13, 46, 47, 49, 50]. For example, in the Helsinki birth cohort [46], men in their early 60s who already knew they had a diagnosis of hypertension in midlife were generally insulin resistant and obese but at birth had been thin and short but had caught up by age 11 years. Others who had previously undiagnosed hypertension were overweight with an abnormal lipid profile. They had been short at birth and had been thin and short at age 11.

Magnitude of the Effect of Programming

Many studies have quantified the relation between BW and later blood pressure, either as absolute differences in mmHg in systolic and diastolic BP or as an incidence of hypertension. Increased BP is more readily demonstrable in adults and may reflect pathophysiological amplification with age [48]. The magnitude of the BP effect ranges from 1 to 10 mmHg on systolic BP and slightly less on diastolic BP during adulthood. Several studies have reported a predominant effect on systolic BP, sometimes with no effect on diastolic pressure, with a resultant higher pulse pressure [48, 51].

Published studies attempting to link birth weight with subsequent BP and the magnitude of the elevation do not necessarily concur. A large prospective US study concluded that there is no relation between birth weight and BP at 7 years

of age in either white or black children [23]. Some studies have reported an inverse relation between blood pressure and birth weight in children [14], even in infants [52]. Yiu et al. reported that in 7-year-olds, there was a 1.3 mmHg decrease in systolic blood pressure and 0.6 mmHg decrease in diastolic blood pressure for each 1 kg increase in birth weight [12]. Others have found no correlation, even in older children [18]. In general, with advancing age, the correlation seems to become stronger and more readily demonstrable. Besides a more subtle impact in young subjects, many other factors, including methods of BP determination and small subject numbers, may account for the lack of statistical differences.

In absolute terms, the magnitude of BP increase in persons who were LBW neonates is small, once analyses are adjusted for confounders, and LBW should, therefore, best be considered as another risk factor for hypertension and cardiovascular disease. However, because of the high incidence of LBW, even a small population-wide statistical increase in mean BP would lead to a considerable number of additional persons being diagnosed as pre-hypertensive or hypertensive by the current diagnostic criteria. The large US studies by Curhan et al. documented a 39–43 % increase in diagnosed hypertension in 25–55-year-old women whose BW was below 5.0 lb and a similar 26 % increase in 40–75-year-old men [9, 10]. A recent meta-analysis of 78 studies reported a 21 % increase in the risk of hypertension in persons of relatively lower BW [53]. Pediatric studies have generally not observed frank hypertension, despite statistical increases in BP, supporting the hypothesis that there is amplification of the pathogenetic mechanisms with age.

In contrast to the epidemiologic data, most experimental animal models of developmentally programmed hypertension have shown a large increase in BP. In rat and murine models, the increase in systolic BP measured by tail-cuff method in adult animals is reported to be 20–30 mmHg above control levels [54–58]. As in humans, the increase in BP does not appear to be present or is only modest early in life [54, 59]. These animal data have come under scrutiny with the introduction of continuous intra-arterial radiotelemetric BP recording in rodents. In some models, the BP increase is only demonstrable with exposure to stress such as physical restraint [60]. In other reports, the effect on intra-arterial BP has been relatively small [57, 61, 62], absent, or even reversed [63]. Increased mean arterial pressure of approximately 6–10 mmHg by direct intra-arterial measurement has also been described in sheep after prenatal steroid treatment [64, 65]. Nevertheless, the large amount of experimental data taken together indicates that developmental programming of BP in association with lower birth weight does occur.

It is important to note that birth weight likely serves only as a crude marker of adverse prenatal environment and is not causally related to the programming phenomenon; this marker phenomenon may explain the mixed results of some of the human experience. As discussed below, much remains to be learned about the pathogenesis of programming.

Potential General Mechanisms of Developmental Programming

Glucocorticoids

Relatively little is understood about the programming signal(s) from the mother or the environment to the offspring. A leading hypothesis states that fetal exposure to excessive glucocorticoid levels constitutes a major programming signal [66]; this concept is supported by the finding of elevated cortisol levels at term in fetuses with intrauterine growth restriction [67].

Under physiological conditions, the fetus is protected from maternal glucocorticoids by the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11βDH2), which metabolizes glucocorticoids into inactive metabolites. High maternal cortisol levels due to maternal stress or glucocorticoid administration may overwhelm the capacity of 11βDH2, allowing the active hormone to cross into the fetus [64, 66]. The long-term effect of glucocorticoid administration to

the mother to accelerate fetal lung maturation has been examined is several studies, with variable results; some investigators have reported increased BP and obesity in the offspring [68], while others have observed no measurable difference [68]. Prenatally programmed hypertension has been induced experimentally in several species by maternal glucocorticoid administration during a sensitive period of gestation [56, 64, 65, 69]. Both negative and positive results have been reported in sheep; the differences may be attributable to the timing of the exposure or the type of glucocorticoid used [70]. Additional work on the maternal glucocorticoid hypothesis is provided by experiments in rats showing that offspring programming of hypertension is prevented or ameliorated by pharmacologic inhibition of maternal glucocorticoid synthesis or by maternal adrenalectomy [71–73].

Increased fetal exposure to glucocorticoids could also result if there is decreased placental 11βDH2 activity. There is evidence that activity of the enzyme may be impaired by maternal stress [74] or by intrinsic placental dysfunction, as seen in preeclampsia [75], and the level of the enzyme activity has been correlated with fetal weight [76]. Administration of a 11βDH2 inhibitor, carbenoxolone, to pregnant rats causes fetal IUGR and programs adult hypertension [55, 77]. Also, surgical reduction of uterine blood flow in rats or embolization of uterine vessels in sheep, either of which may cause placental ischemia and results in programmed hypertension in the offspring [57]. Thus, there is considerable evidence to support a role of fetal glucocorticoid exposure in developmental programming, but other factors may be equally important and require further study.

Epigenetic Imprinting of the Fetal Genome

Epigenetic mechanisms can be defined as heritable changes in gene expression that are not caused by changes in DNA sequence [78–80]. Epigenetic gene regulation is largely responsible for the fact that, despite identical genomes, different cells and tissues of the organism exhibit vastly different phenotypes. Although direct evidence is still scant, it is likely that epigenetic phenomena are operative in developmental programming [81, 82]. Epigenetic regulation can take place via at least three different mechanisms – first, DNA methylation affecting the binding of certain DNA-binding proteins; second, modification of chromatin configuration through methylation, acetylation, or phosphorylation of histone proteins, the "packaging proteins" of DNA; and third, silencing of specific mRNAs by microRNA molecules.

The majority of the embryonic genome is demethylated in the early postconceptual period, followed by large-scale methylation to establish a new methylation pattern, and this process may be susceptible to variations in maternal or paternal diets [83]. Maternal undernutrition during the preimplantation period appears to impair methylation in the embryo [84] and program increased blood pressure in the offspring [85–87]. In addition, paternal undernutrition may also have important effects [85, 88].

Later in gestation, the effects of impaired methylation, as well as changes in histone protein modification and RNA silencing, may be organ specific and depend on the developmental state of the given organ. This may explain why, for instance, maternal protein restriction in the rat during the second half of pregnancy programs a reduction in the number of nephrons [54]. There is experimental evidence that the effects of prenatal programming may be alleviated by maternal treatment with the methyl donor folic acid [89, 90], and preliminary data in humans suggest that folic acid supplementation reduces the risk of low birth weight and prematurity [91, 92]. Possible targets of epigenetic programming relevant to the development of hypertension include the renal 11βDH2 enzyme, renal and adrenal angiotensin II type 1 receptor, and the glucocorticoid receptor [93–96].

Of both interest and concern are the findings that in experimental rat models, the effects of prenatal programming appear to carry across to the next generation [97, 98]. For instance, rat offspring from low-protein pregnancies passed on

the phenotype of low nephron number and hypertension to their progeny via both maternal and paternal lines [97, 98].

Oxidative Stress and Fetal Programming

There is growing evidence that oxidative stress during fetal life may be a major factor in fetal programming [99]. Some of the adverse effects may be reduced by tempol, which is an ROS scavenger [100]. Recently, Chang et al. [101] have shown that hypertension programmed by maternal diabetes could be ameliorated by engineered overexpression of catalase in the renal proximal tubule. In that study, it was shown that the overexpression of the catalase triggered the Nrf–HO-1 defense system.

Maternal and Placental Risk Factors

Maternal Nutrition

Maternal nutrition is well known to affect fetal growth. A variety of maternal nutritional factors have been associated with developmental programming of hypertension (Table 7.1). Most, but not all, are associated with low birth weight. A striking example of overall nutrient restriction is provided by the long-term follow-up studies of people whose mothers were exposed to the Dutch famine in 1944–1945.The global nutrient deprivation lasted for a sharply defined period. As adults, the offspring who were exposed for at least 10 weeks had an increased rate of hypertension and cardiovascular disease [32, 102–104]. Other examples of global nutritional deprivation come mostly from underdeveloped countries. For instance, maternal nutrient status during pregnancy was linked to BP increase in 10–12-year-old Jamaican children [105]. Experimentally, programmed hypertension is inducible by global food restriction in several species, including the rat and the sheep (Table 7.2) [106–108].

Deficiencies in specific nutrients have also been implicated, but the evidence is less clear. As noted previously, folic acid supplementation during pregnancy appears to reduce the risk of fetal growth restriction, but its effect on later blood pressure is not known [109, 110]. Other implicated nutrients include vitamin A [111], zinc [112], iron [113], sex hormones [114], and micronutrients in general [110].

Maternal overnutrition and obesity [115] or high salt intake [116, 117] may also induce later-life hypertension in both human subjects and experimental models.

Table 7.1 Maternal exposures or conditions and prenatal programming

Maternal extrinsic exposures and future hypertension in offspring
Global reduction in protein and calories
Low-protein diet and isocaloric protein restriction
High-salt diet
Vitamin A deficiency
Folic acid deficiency
Iron deficiency
Nephrotoxic drugs
Tobacco exposure
Alcohol exposure
Maternal conditions and future hypertension in offspring
Placental deficiency
Maternal diabetes
Maternal obesity
Maternal CKD

Table 7.2 Animal species for the study of programming

Rodents – rat, mice, guinea pig
Sheep
Nonhuman primates
Good reviews may be found as follows: (a) Nathanielsz [187]; (b) Bertram and Hanson [188]; (c) Ozanne et al. [189]

Other Maternal Factors

There is a reported association between birth weight in persons whose mothers' mothers had either gestational or non-gestational diabetes and later development of the metabolic syndrome and hypertension in the offspring [118]. In particular, larger fetal and newborn size appears to be

associated with increased risk of obesity in later life [119]. One study reported elevated BP in the offspring of such pregnancies as early as at 3 years of age [118]. Other causes of LBW that are associated with later hypertension include maternal smoking [120], alcohol [62], and caffeine intake [121]. Unadjusted data from a cohort study in Western Australia suggested that maternal smoking might be associated with reduced birth weight and, later, with higher BP in young (1–3 years) offspring, but an adjusted analysis that included potential confounding factors ablated the BP effect from low birth weight [120].

Maternal Glucocorticoid Treatment

The long-term effect of glucocorticoid administration to the mother [122–124] to accelerate fetal lung maturation has been examined in several clinical studies, with variable results; some investigators have reported increased BP and obesity in the offspring [122], while others have observed no measurable difference [125]. This is discussed further in Chap. 26. Cortisol and other stress hormones are also implicated by studies linking maternal stress to developmental programming of cardiovascular disease, including the metabolic syndrome and hypertension [126].

Prenatally programmed hypertension has been experimentally induced by maternal glucocorticoid administration in several species, including the rat and the sheep [56, 64, 65, 69]. In both species, there seems to be narrow window of susceptibility to glucocorticoids, during the third trimester in rats and first-trimester sheep; it should be noted that sheep are much more mature at birth. However, not all investigators were able to demonstrate an effect in sheep; the difference may be attributable to the timing of the exposure or to the type of glucocorticoid used [64, 65].

The Placenta and Programming

Preeclampsia and placental dysfunction are the most common causes of LBW in developed countries and has been associated with hypertension in the offspring [57, 127]. Clearly, placental dysfunction has metabolic consequences for the fetus that may contribute to developmental programming [75, 128], but the available data are very limited except for that about the placental 11β-hydroxysteroid dehydrogenase type 2 (11βDH2) enzyme, discussed earlier.

It has been suggested that placental size and size discrepancy between the newborn and its placenta correlates with adult blood pressure [32, 49, 129, 130], but further studies are required to confirm and elucidate this observation.

Programming Targets in the Offspring

Kidney

Much of the research on programmed hypertension has been devoted to the role of the kidney. Experimental data indicate that the three renal compartments – vascular, glomerular, and tubulointerstitial – may all have structural and/or functional aberrations, but the role of the number of nephrons after an in utero insult has received the greatest attention. In humans, kidney development begins during the 6th week of gestation, and nephrogenesis (new nephron formation) is completed around the 36th week of gestation.

Nephron Number

It is well established that diseases that cause extensive renal damage and chronic kidney disease are frequently associated with loss of functioning nephrons and hypertension. The consequent progressive kidney injury is hypothesized to be mediated by increased flow and filtration in the remaining glomeruli, the so-called hyperfiltration theory. There is a wide variation in the number of glomeruli in the human kidney, ranging from 300,000 up to 2,000,000 [131]. It is therefore attractive to speculate that a congenitally low number of nephrons, even in the absence of renal disease, may lead to later hypertension. Strong support for this speculation was provided by an autopsy study by Keller et al. [132] which, though small (ten hypertensive and

ten normotensive persons who had expired due to accidents), indicated that hypertensive young adults without renal disease had a lower number of nephrons than control subjects. Because of the young age of the autopsied subjects, the low nephron count was suggested as congenital [132].

Later studies have confirmed an inverse correlation between number of nephrons and birth weight on one hand and adult BP on the other in American Caucasians. However, interestingly, such correlation was not present in African Americans, who generally have a higher incidence of hypertension [140, 141]. The nephron number per kidney in these studies was measured by the unbiased but cumbersome dissector/fractionator stereological method, explaining the paucity of human studies [131]. This method determines the total number of nephron in the whole kidney in three-dimensional space. More commonly, investigators have employed a counting method in histologic slides, measuring the number of glomeruli in a two-dimensional plane. A possible source of error with this methodology is the change in relative volume of different renal compartments (glomeruli, tubules, interstitium) as a result of intrauterine pathology. However, such histologic studies do in general agree with the stereological method in showing a reduced number of nephrons in LBW babies [133].

A few studies have been done utilizing indirect evidence, using kidney size, measured by ultrasound, as a surrogate for nephron number in children. The results are inconsistent; kidney size was reduced in LBW children in some studies but not in others [134, 135]. Additionally, kidney size may not be a reliable marker of nephron complement because of compensatory hypertrophy. Interestingly, persons born with a single kidney generally do not develop hypertension. Additional human studies are clearly needed to clarify the issue of nephron endowment and subsequent BP.

Experimental studies strongly support the association between the number of nephrons present at the end of nephrogenesis and later hypertension. In several models of genetic hypertension, there is a strong association between congenitally low nephron number and hypertension [136, 137]. However, crossbreeding experiments between spontaneously hypertensive rats SHRs and the normotensive WKY controls hint that filtration surface area, which has been linked to the development of high blood pressure, may not always be related [138]. The study looked at F1 and F2 offspring from this cross. BP was measured weekly from ages 5 to 15 weeks, and the animals were euthanized at 15 weeks, at which time glomerular number, size, and surface area were determined. Although the offspring exhibited the expected wide range of nephron numbers and BPs, no association between the two was noted in the F2 generation, in which there is random segregation of the genes from the WKY and SHR.

That being said, low nephron number has been documented in several experimental models of programmed hypertension and/or IUGR, both by true stereological methods and by other methods. Moreover, neonatal uninephrectomy in the rat induces later hypertension [139].

In summary, although studies in experimental animals do link low nephron count to hypertension, human studies are less conclusive and suggest that additional factors are in play, especially in African Americans.

Renal Vessels

Aberrant renal arterial vasculature has been described in experimental models of programmed hypertension [140, 141], but further studies are needed. Some investigators have described decreased capillary density in the kidney [140], but this too awaits confirmation. Similar information in humans is, to our knowledge, lacking. However, it is reasonable to expect that vascular abnormalities similar to those found in systemic vessels (see below) also apply to the kidney. Indeed, it has been hypothesized that renal microvascular disease may be a primary abnormality in programmed hypertension, leading to tubulointerstitial injury as discussed below [142].

Tubulointerstitial Factors

Renal tubulointerstitial pathology or functional alterations may be important in the genesis of hypertension [39]. It has been proposed that renal tubular transport aberrations, induced by injury to the tubulointerstitial microenvironment, may

underlie many types of hypertension by causing renal dysregulation of sodium balance and chronic volume expansion [39, 143]. Increased salt sensitivity, reported in some in children and adults with low birth weight, supports such dysregulation in prenatally programmed hypertension [144, 145]. Further, upregulated renal tubule sodium reabsorption has been directly documented in a rat model of programmed hypertension [146–148]. Factors involved in the accompanying tubulointerstitial injury may include oxidative stress and inflammation. Indeed, expression of oxidative pathways is upregulated in kidneys in relevant rodent models [149, 150], and treatment with reactive oxygen species scavenger or immunosuppressive drugs has been reported to decrease BP in a rat model [150]. One may speculate that an initial tubulointerstitial injury initiates salt-sensitive hypertension by chronically upregulating renal tubular sodium reabsorption and leading to chronic extracellular volume expansion [151]. Possible causes of tubulointerstitial injury include ischemia due to intrarenal microvascular abnormalities, heightened sympathetic activity, and increases in certain circulating vasoactive substances (see below).

Other factors may contribute to interstitial disease. For example, in a retrospective review, Feig et al. noted that children with incident hypertension had relatively elevated uric acid levels. Additionally, such children had evidence of lower birth weights and displayed markers of endothelial dysfunction [152]. In a pilot study, Feig and colleagues treated youngsters with hypertension and elevated uric acid with allopurinol and noted improved BP. In a subsequent article [153], the authors speculated that abnormalities in uric acid may be involved in aberrant intrarenal microvasculature (see Chap. 5).

The Intrarenal Renin–Angiotensin–Aldosterone System and Programming

The kidney contains a local renin–angiotensin–aldosterone system (RAAS) in which all components are present; this intrarenal RAAS appears to function locally, distinct from the systemic RAAS, contributing to maintenance of normal renal physiology, and also participates in many pathologic states [154]. The intrarenal RAAS is critical for normal kidney development [155, 156]. There is strong experimental evidence that developmentally programmed hypertension is associated with an altered intrarenal RAAS during prenatal life and in the perinatal period. Rat pups born to protein-restricted dams exhibit changes in levels of intrarenal components of RAAS, including increased expression of renin and angiotensin II type 1 receptors, decreased expression of angiotensin II type 2 receptors, as well as decreased angiotensin II levels [59, 93, 157–159]. In ovine models of programming, the administration of glucocorticoids to the fetus or maternal food restriction [160–162] is associated with changes in intrarenal RAAS expression. Similar information is not, to our knowledge, available in human newborns.

Thus, it appears that changes in the intrarenal RAAS occur in developmental programming. Exogenous alteration of the RAAS by administration of an angiotensin receptor blocker in rat pups still undergoing nephrogenesis results in a decreased number of nephrons and later hypertension [163]. Prenatal suppression of the RAAS would also be likely to cause abnormal renal vascular development, and one might speculate that such suppression could lead to tubulointerstitial ischemia and oxidative stress that may ultimately mediate dysregulation of sodium balance.

Renal Nerves

Much data suggest that the renal nerves participate in BP regulation either via effects on renal hemodynamics or on renal sodium transport. Renal denervation has been shown to alleviate severe treatment-resistant essential hypertension [164]. The role of renal nerves in developmental BP programming in humans has not been established, but in a rat model the sympathetic outflow to the kidney appears increased, and renal denervation prevents or ameliorates the development of hypertension [165, 166]. It is attractive to speculate that increased renal sympathetic stimulation, as a part of generalized sympathetic overactivity, is a key element in promoting renal Na by the mechanisms discussed above, hence leading to increased extracellular volume and hypertension.

Systemic Vasculature

Large numbers of human and experimental studies have examined changes in the systemic vasculature in IUGR offspring and whether these could have a role in the development of hypertension. Whether primary intrinsic structural defects are present is not clear. A few human studies have shown decreased reduced arterial diameter in large vessels in adults [167] and [168–170] children with LBW, but others have failed to find any effect of BW on arterial diameters [171, 172]. Arterial stiffness, a possible indicator of an abnormal arterial wall, has also been variably noted in large vessels in humans with LBW [170].

Abnormal vascular endothelial function has been hypothesized as an important contributor to the development of hypertension. Relevant studies have included determination of vascular relaxation in response to increased flow or acetylcholine (endothelium-dependent relaxation) and to NO donor (endothelium-independent relaxation). Impaired endothelium-dependent relaxation was reported in children and adults with LBW [169, 171, 172]. However, some reports show no change [173, 174]. Further, the presence of such changes in some infants and children without elevated BP [175] suggests that the alterations may be a direct consequence of the intrauterine environment rather than hypertension. Of interest, one report documented the presence of such functional abnormalities in subjects whose LBW was due to IUGR but not in others with LBW due to prematurity [169].

In contrast to aberrant vasorelaxation, abnormal vasoconstriction in response to stimuli is not consistently found in humans or experimental models. Microvascular dysfunction was examined in 3-month-old infants in whom skin perfusion was measured in response to acetylcholine or an NO donor. Response to acetylcholine, but not to the NO donor, appeared impaired in LBW infants, a possible evidence of a primary defect in NO-cAMP generation [176]. A study by the same investigators in 9-year-old normotensive children provided similar results [171].

As noted earlier, abnormal uric acid metabolism has emerged as a potential mediator of endothelial dysfunction and hypertension [153] and has been proposed to be important in prenatal programming of hypertension [152]. In addition to alterations in the systemic vasculature, uric acid might promote hypertension via vasoconstriction or other effects on intrarenal vessels.

Thus, there is evidence to support the presence of both structural and functional abnormalities in both the macrovascular and microvascular circulation, but whether these changes result in the development of hypertension has not been unambiguously established.

The Sympathetic Nervous System and Stress

Several studies of human subjects with low birth weight or prenatal stress documented changes in stress reactivity and sympathetic nervous system function in the offspring. For example, when studied at an average age of 58 years, people exposed to the Dutch famine in utero displayed an exaggerated BP response to stress if their prenatal exposure was during early gestation [177]. Reactivity to stress in adult life has been approached by producing mild psychosocial stress and then measuring plasma or salivary cortisol levels before and after the intervention [178–180]. Results have varied. For example, de Rooij et al. found no differences in cortisol responses after stress, while Kajantie et al. [179] reported an inverse U-shaped relationship between cortisol levels and birth weight with psychosocial stress. The lowest ACTH and cortisol levels were observed in the participants who weighed the least at birth.

A study of preteen children showed increased urinary catecholamine excretion in subjects who were born preterm or had evidence of IUGR at term, but there were no differences in baseline or stress-induced BP as compared to control subjects [181].

Stronger evidence that stress reactivity and sympathetic activity can be programmed prenatally comes from experimental studies. Increased BP response to stress has been described in both rats and sheep; however, the baseline BP was not

invariably elevated [182–184]. An exaggerated increase in BP was also described after amphetamine-induced catecholamine release in rats that had been exposed to dexamethasone in utero [183]. Increased cortisol level in response to stress has been described in sheep that had been exposed to betamethasone in utero [182].

Thus, responses to stress appear to be modified by prenatal conditions or exposures in certain experimental models, and there are hints that this may be the case in humans. However, the role of hormones released by stress or of the sympathetic nervous system in the development of hypertension has not been clearly established. Because sympathetic overactivity may be a predictor of future hypertension [185, 186], intrauterine stress may be considered as a possible risk factor associated with prenatal conditioning.

Speculation about Prognosis, Prevention, and Suggestions for Management

Persons who have been born after exposure to an adverse intrauterine environment may be at risk of having undergone perinatal programming. Such people should be considered as having an "extra" risk factor for hypertension and cardiovascular disease, given the growing number or reports, summarized above, which indicate that such persons may develop hypertension and other "programmable" traits such as obesity, dyslipidemia, and metabolic syndrome [185]. Risk for these other conditions may be at least as important as changes in BP. For example, one study reported that CV mortality in LBW subjects is only minimally mediated by BP [185].

Prenatal programming may be avoidable. At this time, there would appear to be sufficient epidemiologic and experimental data to suggest healthful measures that would lower the chance of an adverse intrauterine milieu. Thus, before conception and during pregnancy, mothers should have adequate protein–calorie intake and should avoid smoking and alcohol. Folic acid supplementation still remains controversial with respect to the prevention of future cardiovascular disease, though adequate intake is important for all.

After birth, at-risk children should be followed, but to what extent is not clear. Excessive postnatal weight gain should be avoided, but there are presently insufficient data for guidelines. However, it makes sense to encourage a healthy diet that avoids excessive salt, as well as a healthy lifestyle. Further, monitoring the BP in such children as they mature should permit early intervention if hypertension develops. Currently data are not sufficiently robust to make a recommendation that at-risk children should have their renal size monitored or be screened for microalbuminuria. Further, there are not enough data to indicate whether treatment with ACE inhibitors or ARBs in at-risk persons would be helpful.

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Experimental Models of Hypertension and Their Relevance to Human Hypertension

8

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Abstract

This chapter reviews a variety of models of experimental hypertension with the intent of providing a resource for the interested reader. Much of the important progress in delineating the pathophysiology of blood pressure regulation and the changes that occur in hypertension has been accomplished via animal models. Some models explore normal and abnormal physiology without genetic manipulation but rather by surgery, infusion of medications, and alterations in diet. In other models, inbreeding or genetic manipulation has resulted in increased or decreased blood pressure. These various models should be considered both for carrying out research in hypertension and in evaluating studies that have already been conducted.

Keywords

Experimental hypertension • Animal models • Transgenic • Knockout • Renovascular hypertension models • Consomic • Congenic

Introduction

A substantial amount of progress in the understanding of human hypertension has been achieved through the development of a number of experimental animal models. Ever since the early 1700s, when the Reverend Stephen Hales [1, 2] measured blood pressure 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 normal blood pressure, hypertension, cardiovascular disease, and kidney disease. There are a variety of models – some that explore normal and abnormal physiology, and others in which inbreeding or genetic manipulation has resulted in increased or decreased blood pressure.

There is wide agreement that the best experimental models for the study of human disease should mimic the entity in question in people – in the anatomy, the physiology, and the course of the disease. Thus, useful experimental models

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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 sustainable. This chapter will briefly review some of these models with the intent of providing a resource for the interested reader.

Nongenetic Models of Hypertension

Nongenetic models of hypertension utilize infusion of drugs/substances, or manipulation of the diet or environment to increase or decrease blood pressure, or use surgical procedures to induce hypertension. Depending upon the aims of the intended research, such models (described below) may be important.

Induction of Hypertension with Drugs

Tigerstedt and Bergman, whose work constitutes the major underpinning of cardiorenal physiology, discovered renin and demonstrated in 1898 that the infusion of a crude extract of rabbit kidney markedly increased blood pressure [3]. They hypothesized, "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 only minimal notice until the 1930s, when the importance of renovascular disease as a cause of hypertension became evident. Intense research on hypertension from the 1930s onward has resulted in a large body of knowledge about the renin-angiotensin-aldosterone system (RAAS, also called the renin-angiotensin system (RAS)), described further in Chap. 2. It is now well appreciated that infusion of angiotensin II (Ang II), depending upon the dose and the rate of infusion, can increase BP either acutely or gradually [4]. Further, many basic and clinical studies have employed agents that block or interfere with the RAAS [5–8]. The step at which the complex RAAS is blocked can be used to probe the role of a given component of the system (see Table 8.1 for a list of models that use drugs, surgery, or diet to study hypertension).

Table 8.1 Models of hypertension not involving genes

Surgically induced models of hypertension
1. Renal artery stenosis
2 kidney, 1 clip
1 kidney, 1 clip
Intrarenal aortic clip
2. Wrapped kidney-Page kidney
3. Coarctation of the aorta
Pharmacologic models of hypertension
1. Angiotensin II infusion
2. DOCA
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

Additional hormonal systems also can affect blood pressure, for example, endothelins, nitric oxide and its metabolites, catecholamines, and natriuretic peptides. Nitric oxide is a key substance in controlling peripheral vascular resistance via its vasodilatory effects [9]. The inhibition of NO synthase with L-NAME, for example, results in hypertension that is accompanied by marked peripheral vasoconstriction [10, 11]. 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 [12–14]. 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 blood pressure; additional vasoactive substances may well be discovered, and infusion studies are helpful in learning more about each such substance.

Surgically Induced Models of Hypertension

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. 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) [15]. 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.

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 [16–23]. In dogs, the 2K, 1 clip model produces elevations in blood pressure over several days, and the blood pressure level plateaus thereafter. However, between 10 % and 20 % of the animals spontaneously have a decrease in their blood pressure 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.

There are several anatomic variations of this renovascular model of hypertension – using clips on both renal arteries (2 kidney, 2 clip) or using 1 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 [20].

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 [23].

Hypertension from Perinephric Compression

In 1939, Irwin Page developed a model of hypertension in the dog that in which perinephric renal pressure was increased by simply wrapping one kidney with cellophane (often called the "Page kidney") [24]. 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. 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 [25–27]. In a model in which one kidney is removed as well as two third of the remaining kidney (subtotal nephrectomy – five sixth 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 blood pressure.

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 [28].

Neurogenic Hypertension

The central nervous system modulates blood pressure and can be involved in the production of hypertension [29]. A number of denervation techniques have been employed to investigate

central mechanisms of hypertension. Sinoaortic baroreceptor denervation is the most commonly used method and results in predictable hypertension [30]. The technique was first reported by Krieger in 1967 [29] 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 blood pressure [31–33]. 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 [34, 35].

Clinical hypertension may be salt sensitive [36] and high salt intake in some strains of animals leads to hypertension, as in the Dahl salt-sensitive rat strain [37].

The ingestion of increased fructose in the diet also leads to hypertension in animals. Studies 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. 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, as well as its interaction with uric acid [38].

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 [39–50]. 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 blood pressure [39]. A few years later, the development of the spontaneously hypertensive rat (SHR) was reported [40]. There are multiple other rat strains associated with hypertension – the Dahl salt-sensitive rat and salt-resistant rat strains [41], the Milan strain [41], and the Sabra [43] and Lyon [44] strains. A stroke-prone strain has been developed from the SHR strain [45].

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 [51]). 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 list of inbred rat strains is found in Table 8.2.

A further refinement of inbred strains is the use of congenic and consomic strains [52–56]. 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. 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. It generally takes ten generations of backcrosses to attain a congenic strain.

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 chromosome that differs by being replaced using serial backcrosses that are marker assisted.

Recently Flister et al. [57] 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 home in on several BP loci of interest. They found that transferring a 6.1 Mb portion of SS chromosome 12 confers salt-sensitive hypertension.

Table 8.2 Models of genetic hypertension well-characterized hypertensive rat strains and controls

Rat strain	Phenotype	Control strain	Background	Reference
Spontaneously hypertensive rat (SHR)	Hypertension by age 4 weeks	Wistar-Kyoto (WKY)	Wistar	[40]
Stroke-prone SHR	Bred from SHR; prone to stroke		SHR	[45]
Dahl salt-sensitive	Hypertension with salt loading	Dahl salt-resistant	Sprague-Dawley	[41]
Milan hypertensive (MHS)	Bred as model for studying cation transport	Milan normotensive (MNS)	Wistar	[42]
New Zealand genetically hypertensive		Controls generally unselected	Wistar	[39]
Sabra hypertensive (SBH)		Sabra normotensive (SBN)	Unknown/unclear	[43]
Lyon hypertensive rat	Low-renin hypertension	Lyon normotensive and Lyon low blood pressure	Sprague-Dawley	[49]
Fawn-hooded hypertensive rat	Hypertension, kidney disease, and platelet abnormalities		German brown × white Lashley	[46]
Prague hypertensive rat		Low BP Prague strain	Wistar	[47]
Russian inherited stress-induced arterial hypertensive rats (ISIAH)	Stress-induced hypertension		Wistar	[48]

Sexual Dimorphism Models

A number of the phenotypically bred models of hypertension exhibit sexual dimorphism and thus lend themselves to the study of different expression in males and females [58–61]. For example, hypertension and cardiovascular disease are more pronounced in male SHR [59–72].

In the Sabra rat, there appear to be QTLs (quantitative trait loci) for salt sensitivity expressed on chromosome 1 that differ by gender [55]. These are SS1a and SS1b in male rats but only SS1b in females.

Murine Models of Hypertension

Mendelian Models

The resorption of salt and water by the kidney importantly regulates blood pressure, 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 [62]. 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 [63]).

Transgenic, Knockout, and Knockin Models

The role of the RAAS and other hormonal systems in hypertension has been extensively studied with the use of transgenic, knockout, and knockin models [63–68]. 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 [66]. Fulminant hypertension develops in this animal early in life. Knockout animals have a given gene ablated, while knockin animals contain additional copies of a gene of interest. A variety of transgenic, knockout, and knockin animals have been developed that have been used in studying hypertension. For example, mice transgenic for the rat angiotensinogen gene become hypertensive [68]. There are also mouse transgenic for renin [69] and other components of the RAAS (Reviewed in 63 and 71) [63, 70]. 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 [71]. 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.

Developmental Origins

The influence of the intrauterine and perinatal milieu on later hypertension has been studied in a number of animal models – particularly in murine and rat models, as well as in sheep, guinea pigs, and other species. These models are discussed in Chap. 7.

In Vitro Models of Hypertension

There are many unique approaches to the study of hypertension that involve in vitro experiments (Reviewed in 2012 by Cook and Re) [72]. 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.

Implications

The choice of an appropriate model of hypertension depends on the research question one wishes to study. It is hoped that this brief outline of available models and concepts underlying their development may be a starting point for the reader's consideration.

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Part II

Assessment of Blood Pressure in Children: Measurement, Normative Data, Epidemiology

Casual Blood Pressure Methods

9

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Abstract

The diagnosis of hypertension in children or adults is predicated on the accurate measurement of the blood pressure and the proper interpretation of that measurement. Outside of the hospital setting, blood pressure is measured noninvasively, that is, not using indwelling arterial lines. The generally agreed-upon term for noninvasive BP measurement outside of a strict study setting and while the patient is at rest is the "casual blood pressure." This chapter will review currently available methods of casual BP measurement and identify the advantages, disadvantages, and pitfalls of these methods.

Keywords

Oscillometry • Auscultation • Casual blood pressure • Observer • Beat-to-beat variability • Korotkoff sounds • Aneroid • Sphygmomanometer – manometer • Validation

The cost of hypertension in the United States in 2010 was predicted to be $93.5 billion, based upon estimates of utilization of health-care services, medications, and missed days of work [1]. The pediatric piece of this total cost is likely only a small percentage, but still represents a significant cost, which has been rising over the past decade [2]. The long-term health-care issues of undetected hypertension [3] in children are not clear, but would logically include a significantly increased rate of cardiovascular and cerebrovascular events as affected children become adults. Given the medical and economic impact of hypertension, establishing a diagnosis of hypertension in a child is something that needs to be done carefully; the providers making this diagnosis must understand the process of

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measuring BP and the pitfalls associated with these measurements.

Blood pressure measurements obtained on children were first reported in 1903 [4]. The authors used a cuff/bladder that could have its size modified using hooks and eyes, and obtained their readings using palpation of the brachial artery. They reported systolic pressures between 75 and 90 mm Hg during the first 2 years of life and 90–110 mm Hg during early childhood. Larger studies in children using more "typical" auscultatory methods were not reported for another 50–60 years [5]. Over ensuing decades, BP methods have evolved from the mercury manometer to aneroid gauges and importantly from these auscultatory approaches to automated or semiautomated oscillometric devices.

The measurement of blood pressure in the office or "casual" setting, which is opposed to measurement in a continuous or near-continuous fashion, such as in an operating room or in a patient with an arterial line, is a complex task that involves several major components: the observer, the patient, and the device. This chapter will focus on the device aspects, but will also address issues associated with observers and subjects having their BPs measured.

Measurement of blood pressure is recommended for children over 3 years of age whenever they present for a health-care encounter and in children less than 3 years of age under special circumstances [6]. In children, the diagnosis of hypertension is based upon correct measurement and then comparing the result obtained with tables developed from large series of readings obtained in children of many ages and heights. Given the lack of "hard" cardiovascular end-points in children, the diagnosis of hypertension in pediatrics is a statistical one. Children with repeated, sustained BPs greater than the 95th percentile for age, height, and sex are considered to be hypertensive. Since blood pressure values tend to drop in most patients on repeated measurement, roughly 1–3 % of all children have been found to be hypertensive when large groups were assessed.

The Measurement: Observer, Patient, and Device

There are three major aspects in the measurement of a person's blood pressure.

Observer: There are many device/method-specific issues that relate to the observer. The observer needs to be trained in the proper use of the device and understand the method sufficiently to recognize valid from invalid readings. It is the observer's responsibility to identify the patient-specific issues described below. In addition to device selection, the observer needs to ensure that an appropriate cuff size is chosen. The size written on the cuff (e.g., "Child"), often will be nonspecific and is assigned by the manufacturer, rather than being driven by data and/or standards. The observer must have the necessary senses (predominantly vision and hearing) and short-term memory capacity to perform the task.

Patient: The patient/child who is to have his or her blood pressure measured is, obviously, a living being. Beat-to-beat variability of systolic blood pressure in people at rest has been reported to be ~4 mmHg [7]. Chronobiologic (day-night) changes in BP are even greater. A BP value determined at any time of the day, even if performed "perfectly," is only truly valid for that moment.

There are certain physiological principles that cannot be ignored as they pertain to the measurement of blood pressure. There are four common methods for BP measurement: direct intra-arterial monitoring, palpation, auscultation, and oscillometry. Each of these methods actually measures a different thing. Each measurement is a surrogate for "true" blood pressure, so these different measures always correlate closely, but they do differ. Assuming that direct measurement in the descending aorta reflects the true BP, direct intra-arterial values obtained from peripheral arteries tend to yield higher systolic values and lower diastolic values and of course have no place in casual BP measurement. Palpation can only be used to determine systolic BP; the ability to palpate a pulse distal to a BP cuff requires a sufficient volume and force of blood, which typically occurs several beats after indwelling lines can sense the resumption of flow as the cuff is deflated. Auscultation relies on the Korotkoff sounds, which are not completely understood, but relate to cuff-induced turbulence in arterial flow [8]. The onset of the first Korotkoff sound,

which is accepted as the systolic pressure, generally occurs between when an indwelling line would sense flow and when the pulse wave could be palpated. Oscillometric devices are described in greater detail later in this chapter.

Devices: There are a large number of potential permutations and combinations that can be compiled to create a BP measuring device. At the most basic, such devices need a cuff to encircle the arm (current convention is still to measure the BP at the upper arm), tubing to connect the cuff to the rest of the device, a mechanism to rapidly inflate and slowly deflate the cuff, a manometer for measurement, and some sensing device to listen to or "feel" blood flow as it resumes with cuff deflation or, in some devices, cuff inflation.

Cuffs: One of the most difficult issues associated with the measurement of blood pressure in children is selection of the proper size cuff. This is an area that is dependent more on opinion and convention than on strong evidence. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents recommends that the bladder of the cuff has a width that is approximately 40 % of the arm circumference midway between the olecranon and the acromion. Assuming a cuff bladder width to length ratio of 1:2, this corresponds to a cuff bladder that will cover 80–100 % of the arm circumference [6]. The British suggest three cuffs (4×13 cm, 10×18 cm, and 12×26 cm) for use in children from 0 to 14 years of age [9].

There is wide variety of pediatric BP cuff sizes in the United States due to the absence of clearly defined standards. AAMI and AHA standards call for a cuff width to arm circumference ratio of 0.4 for patients of all ages and for a bladder length to arm circumference ratio of 0.8. Arithmetically, this mandates a minimal bladder width to length ratio of 1:2, but this ratio has only been recommended [6], not mandated. Consequently, there is wide variability in commercially available cuffs for children.

Undercuffing, the use of too small a cuff, leads to erroneously high BP measurements. Less well established is the converse – overcuffing. A few papers suggest that a cuff that is too wide for the arm will underestimate true BP. Overly long cuffs, those that overlap, do not seem to generate significant errors [10].

Auscultatory Measurement of BP

There are many issues which must be addressed carefully for proper use of auscultation to measure BP. The observer must have adequate hearing and be experienced in the recognition of Korotkoff (K) sounds. The room must be quiet. Normally, observers must be trained and periodically retrained by either recorded teaching materials or in comparison to "experts" in the techniques. This latter method is usually accomplished by the use of a stethoscope with two sets of earpieces. The trainee records his/her values blindly and those data are compared to the values recorded by the "expert." There is no formal tolerance data for an acceptable difference, but the systolic (S) and diastolic (D) BPs should match within a few mmHg.

The American Heart Association Scientific Statement by Pickering et al. from 2005 reviews the techniques and protocol for auscultatory BP measurements in humans [11]. It is generally accepted that K sounds are more easily heard with the bell of the stethoscope. It is important that there be only light pressure applied, so as not to tense the skin tightly and make the bell function more like a diaphragm. There is universal agreement that K1 is the best estimate of SBP. The observer must be careful not to assign K1 to an extraneous sound; sequential K1 sounds for the next few cardiac cycles reassure the observer that the assigned K1 is the accurate SBP measurement, although some patients do manifest an auscultatory gap. In adults, the disappearance of K sounds, K5, is thought to represent the most accurate estimate of DBP. There are few data in children that address this issue. In 1965, Moss and Adams compared auscultatory BP to intra-arterial measurements during cardiac catheterization [12]. Those data and their previous work [13] led them to recommend that K4 (muffling of sounds) be used in children to estimate DBP.

The original [14] and two subsequent Task Force reports continued to make that recommendation. In 2004, the Fourth Report authors [6] changed their DBP recommendation to use K5 in all humans, despite the absence of new data assessing accuracy collected between 1965 and 2004. It is also not uncommon that, in children, K sounds are audible to BP values close to or at zero mmHg. Clearly K5 cannot be used in these children. Data from the Bogalusa Heart Study have demonstrated a superior predictive value of adult hypertension for K4 versus K5 [15].

Another general issue in the manual auscultatory measurement of BP is terminal digit preference. There are observers who assign values which end in a zero or a five much more commonly than other terminal digits. This issue should be addressed in the original training and the retraining of every observer. In addition, the manometer needs to be placed in such a place as to avoid the risk of error due to observer parallax.

The Mercury Sphygmomanometer

Worldwide, there has been a campaign to ban mercury for all uses in response to the mercury levels observed in our environment. While the contribution to the environmental burden from mercury sphygmomanometers is not known, it realistically cannot represent more than a few thousandths of a percent. Nonetheless, it seems unlikely that widespread use of mercury manometers will return. Mercury sphygmomanometers are very ruggedly built and it is, in fact, difficult to release the mercury from the tubing or reservoir.

Periodic maintenance of a mercury manometer is necessary. The filter must be kept clean. The bulb, tubing, and release valve must be kept in proper working order. Only some medical institutions have mandated safely inspections of manometers; routine periodic maintenance protocols must be developed. A mercury manometer which is properly maintained does not require calibration, since the density of mercury cannot change, and differences in atmospheric pressure at varying altitudes do not significantly affect readings.

The Aneroid Sphygmomanometer

An aneroid manometer uses a set of bellows, springs, and gauges to reflect the pressure in the cuff/tubing system. Aneroid devices can be manufactured to very high accuracy levels. In addition to manual aneroid devices, there are electronic versions. The major concern about the long-term use of aneroid manometers is the issue of maintenance and recalibration. In order for BP values obtained using an aneroid device to be accurate, the manometer must be kept calibrated; a frequency of service of no more than every 6 months is recommended. One of the simplest methods to quickly assess the lack of calibration of an aneroid manometer is to verify that the needle is not pointed to 0 mmHg when the manometer's valve is open.

Patient/Subject Preparation

To obtain a BP which represents an accurate, resting value, the practitioner must follow a protocol consistent with that used to develop the comparative standard blood pressure tables [11]. The child needs to be sitting at rest for at least 5 minutes. This may be difficult to accomplish in a busy outpatient setting, but is critical. The BP cuff cannot be wrapped around clothing; it must be applied over bare skin. The child should avoid caffeine-containing beverages and/or use of tobacco for at least 30 min before testing. The child should be seated on a chair with a back, not on an examination table. The arm on which the cuff is placed needs to be supported from below at the level of the heart. His/her legs should be uncrossed. The child must not talk during the measurement; the individual taking the reading should not ask questions during the process. A history of medications with vasoactive properties (antihypertensives, decongestants, nutritional supplements) should be taken.

Most experts recommend taking several readings during each assessment [11]. Frequently, the initial reading, which may be high because of anxiety and the alerting reaction, is discarded, and the clinically acceptable BP value is determined by averaging the second and third reading, separated by at least 1 min. Because of the "white coat" effect, discussed elsewhere, manufacturers

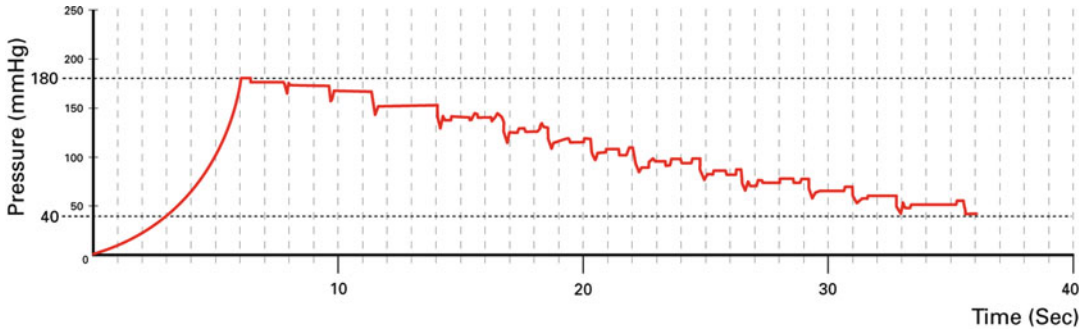

Fig. 9.1 Pressure curve showing BP cuff inflation and deflation for single BP measurement. The BP cuff is automatically inflated by the pump when the BP measurement is initiated, the cuff pressure increases to 180 mmHg over 6 s, the pump stops, and the electronic valves control the deflate from 180 mmHg to a pressure below diastolic. The total measurement time is approximately 36 s

have developed automated monitors which will take multiple readings automatically with no medical personnel in the room. To date there is no large dataset to show the effectiveness of this technology in children.

Oscillometric Measurement of BP

Oscillometric blood pressure devices have gradually replaced auscultatory manometers over the past two decades due to their ease of use and in response to the aforementioned environmental concerns over mercury. Oscillometric devices are also replacing aneroid sphygmomanometers in medical centers and, to a lesser extent, in doctors' offices. Individuals with minimal medical training can reliably operate oscillometric devices. A proper understanding of how oscillometric blood pressure devices work and of their advantages and limitations will enable a health-care provider to more effectively address a patient's blood pressure concerns in a variety of clinical settings.

Unlike auscultatory BP measurements, in which the surrogates for systolic and diastolic pressures are directly identified, oscillometry *calculates* a person's systolic and diastolic blood pressures. There is no specific oscillometric pulse amplitude that correlates with the first or last Korotkoff sounds. Each manufacturer of oscillometric blood pressure monitors uses its own proprietary algorithm to calculate a patient's systolic and diastolic blood pressures.

An automated oscillometric blood pressure device consists of a cuff, a pump, valves, a power source, and various electronic components, including a microprocessor. The typical oscillometric device will automatically inflate the cuff and then gradually deflate the cuff to a pressure below diastolic (see Fig. 9.1). The target pressure for the cuff inflation in Fig. 9.1 is 180 mmHg. Once the cuff is inflated to the target pressure, the cuff pressure is decreased in a controlled manner using a valve. The pressure maybe decreased in a linear manner, or it may be decreased in a stepwise manner using an electronic valve. The step method uses a valve that opens for milliseconds and allows enough air to escape from the cuff so that the cuff pressure decreases by 5–10 mmHg. Once the cuff pressure drops, the monitor will commonly maintain constant cuff pressure for two heartbeats, allowing the device to record two oscillometric pulses. Using the linear method, the cuff pressure will decrease at a steady rate from the target inflation pressure to a point below the diastolic pressure; an oscillometric pulse will be recorded at each heartbeat.

Typical devices intended for adult use will initially inflate to 160 mmHg to 180 mmHg. Devices with a neonate mode will initially inflate to between 70 and 120 mmHg, and devices that have a pediatric mode will inflate to between 120 and 160 mmHg. If the device does not inflate

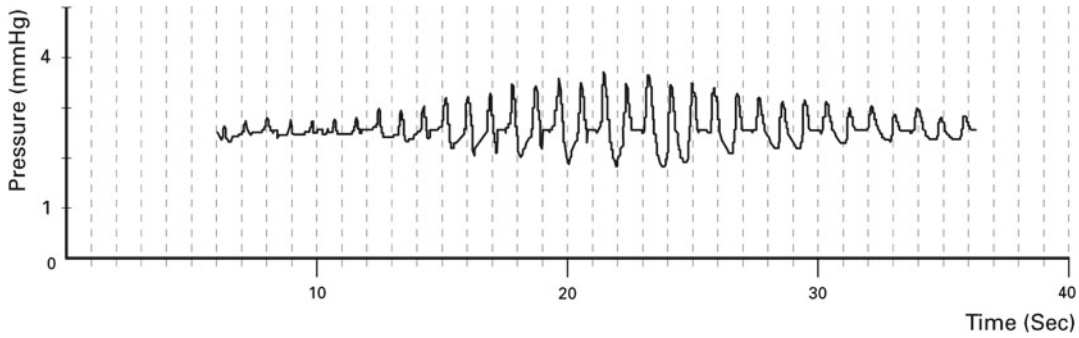

Fig. 9.2 Amplitude of oscillometric pressure pulses with relation to time. The y-axis shows the oscillometric pulses that were collected in the measurement shown if Fig. 9.1. The x-axis shows the time scale corresponding to Fig. 9.1. No data is collected during the cuff inflation, oscillometric pulses are collected at each pressure step, and the pulses are recorded with respect to time

high enough on the first attempt (i.e., the sensor detects oscillations consistent with persistence of arterial flow), the unit's software will reinflate the cuff to a higher pressure. Many devices have an adjustable setting to allow the user to select the initial inflate pressure. The ability to lower the initial inflation pressure is a helpful feature for devices used in pediatrics, as the lower inflation pressure will be more comfortable for the patient and it will result in a faster reading. All devices are required by national and international regulatory standards to have a maximum inflation pressure below 300 mmHg for the adult mode and 150 mmHg for the neonate mode, and all devices are required to have a maximum time limit of 180 s for a single reading in adult mode and 90 s for a single reading in neonate mode, after which point the pressure in the cuff must be released. The regulatory standards do not require any specific safety features for the pediatric mode, although some device manufacturers have implemented thresholds between the adult and neonate limits for pediatrics.

When the cuff is inflated on the patient's limb and the artery is partially or fully occluded, pressure oscillations created by the expansion of the arterial wall during each heartbeat are sensed by the cuff and measured by the device's hardware and software. Near the systolic pressure, the pressure oscillations are very small, and they increase in amplitude as the cuff pressure reaches mean arterial pressure (MAP). The pressure oscillations then decrease as the cuff pressure decreases from the patient's MAP to pressures below diastolic.

Figure 9.2 shows a typical set of oscillometric pulses collected on a healthy adult during the deflate cycle of an oscillometric monitor. The amplitude of the oscillometric pulses starts out at less than 1 mmHg, then increases in amplitude to approximately 3 mmHg at the midpoint of the curve, and finally decreases to less than 1 mmHg at the end of the curve. Once the cuff deflation is completed and the recorded oscillometric pulses are processed, an envelope curve is created using the amplitude of the oscillometric pulses. Figure 9.3 shows the envelope curve for the oscillometric pulses shown above.

The envelope curve in Fig. 9.3 shows the oscillometric pulse amplitude on the y-axis, with these pressures corresponding to the amplitude of the pulses in Fig. 9.2. The x-axis is the cuff pressure for each specific pulse. The curve in Fig. 9.1 shows the relationship between cuff pressure and time. This allows each oscillometric pulse in Fig. 9.2 to be referenced to a cuff pressure.

The envelope curve is the basis for all calculations used to determine systolic and diastolic pressures. Following the curve from left to right, the pulse amplitude increases as the cuff pressure decreases, from 140 mmHg to approximately 90 mmHg. The peak of the envelope curve is the point of maximum oscillation, or the point where the oscillometric pulses reach their maximum amplitude; this cuff pressure correlates with

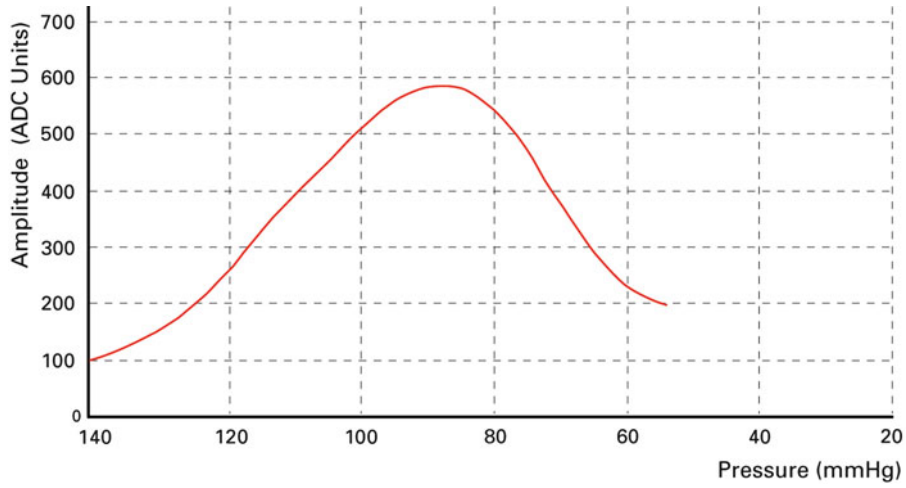

Fig. 9.3 The relationship between oscillometric pulse amplitude with respect to cuff pressure is shown. The y-axis shows the amplitude of the oscillometric pulses. This envelope curve is created by recording the oscillometric pulse amplitude for each pulse with respect to time. The x-axis in the plot is cuff pressure, not time. The relationship between cuff pressure and time is shown in Fig. 9.1. For each point in time, a corresponding cuff pressure is calculated from the plot in Fig. 9.1 and that pressure is used in the x-axis in Fig. 9.3

MAP [16]. As the cuff pressure continues to decrease, the envelope curve falls as the oscillometric pulses decrease in amplitude.

Each manufacturer has its own proprietary algorithm to determine systolic and diastolic pressures. Some manufacturers use pulse amplitude based on a percentage of the maximum amplitude, while others use the slope of the rising and falling portions of the envelope curve to calculate systolic and diastolic pressures, respectively. Many manufacturers use a combination of calculations based on the slope of the curve and amplitude of the pulses. The basis for these calculations typically uses empirical data collected on large populations. Most oscillometric algorithms start by measuring MAP as the peak of the envelope curve and use the approximation:

MAP − 1/3 (PP) = diastolic

MAP + 2/3 (PP) = systolic

Pulse pressure (PP) = systolic − diastolic

Because MAP is the only pressure that can be measured from the oscillometric envelope curve, it is critical that the algorithm is able to determine an accurate value for MAP. Once MAP is determined, it is still necessary to calculate one or more of the three pressures: systolic, diastolic, and pulse pressures.

Some medical conditions, such as pediatric obesity or diabetes, can pose particular problems for oscillometric BP reading, and so manufacturers need to consider large patient populations when developing their algorithms. Significant differences between populations, such as adult and pediatric, may also pose problems for some oscillometric algorithms, and some algorithms may not be properly validated for hypertensive or hypotensive patients. Unfortunately, poorly performing algorithms often will not perform well on the populations that have the greatest need for accurate blood pressure monitoring.

Even small movements of the patient can also adversely impact automated oscillometric measurements. The oscillometric pulses that are detected in the cuff are typically less than 4 mmHg, while small movements of the arm can create spikes in pressure of 10+ mmHg. The oscillometric algorithm's ability to filter motion artifact from the actual oscillometric pulses is critical in situations such as emergency transport or, postoperatively, when the patient may be shivering. Filtering motion artifact is important in the context of this book, when a device is applied to young children, who may have trouble sitting still, or to infants and toddlers who may move to "escape" the squeezing on their arms.

There are several types of automated oscillometric BP monitors on the market, and there are a large number of manufacturers. The variation in the types of monitors is differentiated by what site is used to take the reading. The most prevalent and most widely accepted oscillometric monitors take the BP measurement on the upper arm, occluding the brachial artery. Wrist monitors, however, have become popular over the past 10 years because of their relatively low cost and because one cuff size accommodates a wider percentage of the population. Wrist monitors, however, are not typically considered appropriate for clinical use [17]. There are also specialty monitors that take measurements on the finger or on the forearm, but these are not commonly used in a typical clinic or hospital setting, and validation criteria for these have not been generally accepted.

Several manufacturers have developed oscillometric technologies that take the BP measurement during cuff inflation. This method provides a few advantages: the reading can often be done in less time; and the cuff may not need to be inflated as high, because the inflation can be stopped just above the systolic pressure. Both of these advantages are helpful when taking BP readings on pediatric patients. However, a drawback of taking BP measurements during cuff inflation is that the algorithm will typically be less motion tolerant.

Almost all oscillometric devices also provide a measurement for heart rate. Referring to Fig. 9.2, one can see how the device can easily measure the time between oscillometric pulses and calculate the heart rate.

The blood pressure cuff itself is a critical part of the automated oscillometric blood pressure monitor, as it not only occludes the artery, as in an auscultatory measurement, but is also used as a sensor to measure the oscillometric pulses. A cuff used with an oscillometric device should meet the same AHA guidelines [11] for bladder size and range as an auscultatory blood pressure cuff; this will ensure that the cuff properly occludes the artery. In addition, the cuff may need to meet construction requirements from the oscillometric monitor manufacturer to ensure that it works well as a sensor. All cuffs are required to indicate the limb range for which they are intended to be used, and most cuffs will have a range marker that clearly shows that it is the proper size when it is wrapped around the limb. Cuffs made for use on the upper arm will also be labeled with an artery marker that should be placed over the brachial artery. Proper cuff placement is even more important for oscillometric devices than auscultatory devices, since the cuff bladder is being used as the sensor to measure the oscillometric pulses. If the cuff bladder is not properly located over the artery, the oscillometric pulses may not be properly measured.

Oscillometric BP devices are commonly used in home settings, and most of these devices were developed for monitoring hypertension in adults. Many of these monitors may work on children, but accuracy cannot be assumed if pediatric validations of these devices are not performed. The range of cuffs tested for use with a specific monitor is another important consideration when selecting an automated device. A device intended for use on pediatric patients should have cuff sizes that range from infant through large adult. The literature that accompanies the device should cover the intended populations for the device, and the manufacturer should have information available as what validation protocols the device has passed. In previous years there were several standards used by manufacturers: AAMI SP10 [18], the BHS protocol [19], and the European EN1060-4 [20]. There is currently one international standard for noninvasive BP validations, the ISO 81060-2 [21]. This standard has recently been accepted by the FDA and by the European Union. All new devices sold in the United States and Europe are required to pass the ISO 81060-2 standard; older devices were required to pass one or more of the previous standards to be sold in the United States or Europe. When purchasing a device, it is advisable to look for one that has been tested according to accepted validation protocols and to confirm that the device was validated on pediatric subjects. Some manufacturers also have their devices validated by third parties and have the validation study published in a peer-reviewed journal. Additionally, manufacturers may go further and validate their monitors on special populations to improve the overall performance of

their devices. A thoroughly validated device is the best indication that it will perform well on its intended population.

Automated oscillometric BP technology has several benefits over the manual auscultatory technique, the main advantage being ease of use. The operator has to ensure only that the correct cuff size is used, the cuff is properly applied to the limb, and the subject is properly seated. Automated oscillometric devices can provide a simple, reliable method of taking accurate BP measurements in most clinical and home settings. They are not susceptible to terminal digit preference or other human errors, and there is no person-to-person variance – it operates consistently each time. Low-cost oscillometric home units have also been sold to millions of people around the world, helping individuals take an active part in their own health care. Conversely, poorly performing oscillometric devices on the market can adversely affect a large percentage of their intended population, particularly compromising the health of those in greatest need of accurate BP monitoring, such as hypertensive, diabetic, or bariatric patients. BP units sold in the United States and Europe commonly meet at least one of several validation protocols; this provides some assurance that a monitor performs adequately on a general patient population. Not all marketed devices have been validated, and fewer have been studied in children. The authors recommend that buyers should ensure that a device has been validated in the targeted population prior to purchase.

Conclusion

Pediatric providers should measure blood pressures at every health-care encounter. Performing the measurements requires an understanding of the way the device to be used works, of the potential strengths and weaknesses of the device, of the ability to select a proper cuff size, and of an ability to interpret the result obtained. Auscultatory measurements, using either a mercury manometer or an aneroid manometer, have the advantage of yielding results that can be directly compared with the epidemiological data that have been used to define normal blood pressure and hypertension in children. Oscillometric measurements are generally easier to obtain and correlate well with auscultatory measurements.

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Blood Pressure Norms and Definition of Hypertension in Children

10

Bonita Falkner

Abstract

Prior to the 1970s, measurement of blood pressure was not a standard practice in asymptomatic healthy children. Detection of high blood pressure in children occurred when blood pressure was measured in symptomatic and clinically ill children. 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. It was also recognized that there was progressive increase in blood pressure levels in healthy children 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. Data from these studies have been combined and analyzed to determine the normal distribution of blood pressure levels in healthy children and adolescents. The resulting normal blood pressure range in healthy children from 1 to 17 years of age has become the blood pressure norms on which current definitions of hypertension and prehypertension in children and adolescents are based.

Keywords

Blood pressure • Hypertension • Prehypertension • Children • Adolescents • Growth

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

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in obtaining reliable measurements and the general belief that hypertension was a rare problem in children [1]. Since measurement of blood pressure had not yet become routine, high blood pressure was detected only when significant clinical signs or symptoms were present. Due to 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 on what is 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.

Looking back on this practice, one can understand how some beliefs in medicine develop. With regard to childhood hypertension, the belief had been 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 physical development, this belief has changed. We now have blood pressure data and a body of 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 warrants further evaluation. Some children, especially younger children, do indeed have hypertension secondary to an underlying disorder such as renal disease. 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 35 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. This chapter will review that process, and to a large extent, is a historical reflection on what has transpired. The questions and concerns expressed by the authors of the early reports are important to remember because those are the thoughts that moved this process forward and provide a model to continue the forward process.

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 [2], 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 56 % of cases that died, the average duration of survival following diagnosis of the hypertension was only 14 months. The review of this sample of severe childhood hypertension indicated 90 % mortality within 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 that was clearly 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 issue of childhood hypertension focused on the evaluation for underlying disease and search for 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 frequent 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 [3]. In a review article in 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 [4–8] 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 in the young ranged from 1 % [8] to 12.4 % [7]. Table 10.1 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. These early reports, on hypertension in adolescents and young adults, defined hypertension according to a blood pressure level that was similar to values used for adults [4–6, 8]. The report by Londe [6] was based on an examination of younger children, aged 4–15 years, and 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 [6, 7]. 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,

Table 10.1 Reported prevalence of hypertension in persons 25 years of age or less prior to normative data[a]

Authors	Subjects' age (year)	Number screened	Position in which pressure was taken	Definition of hypertension (mmHg)	Prevalence (%)
Masland et al. [4]	"Adolescents"	1,795	Not stated	140/90	1.4
Boe et al. [5]	15–19	3,833	Sitting	150/90	3.01 males
					1.04 females
Heyden et al. [6]	15–25	435	Sitting	140/90	11.0
Londe [7]	4–15	1,473	Supine	Systolic or diastolic >90th %	12.4 males
					11.6 females
				Systolic or diastolic >95th % (repeated measures)	1.9
Wilber et al. [8]	15–25	799	Sitting	Systolic > 160	1.0
				Diastolic > 90	1.5

[a]Adapted from Ref. [3]

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 95 percentile on repeated measurement is very close to more contemporary estimates of pediatric hypertension derived from far larger numbers of children.

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. [9] 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 7,400 persons who were in 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 age 16 years of age, 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 age 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 BP that marks an increase in cardiovascular events and mortality. This definition continues to be systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg [10–12]. These numbers are the approximate blood pressure levels above which the risks for morbid events are 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 systolic blood pressure. Data derived from the Framingham Study in adults show that blood

pressure in the 130/85–139/89 mmHg range confers more than double the absolute risk for total cardiovascular events following 10 years, compared to blood pressure <120/80 mmHg [13]. 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 [14]. 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 Master et al. is the earliest to show that the normal range of blood pressure is lower in persons aged 16–19 years than that of older adults. Of most significance is that Master 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.

The question that remained unanswered until the early 1970s was what the prevalence of hypertension in children and adolescence is. This question could not be answered without a uniform and consistent definition of hypertension in the young. Moreover, the 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 [6, 15–18]. 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 [19]. It was also recognized that due to differences in measurement techniques, there was likely to be considerable variability in what data were available.

Efforts to gain a better understanding of the occurrence of hypertension in the young initially tended to focus on adolescents. Based on a careful examination of her own clinical data derived from children and adolescents she had evaluated for blood pressure elevation, Loggie [3] suggested that essential hypertension was more common in adolescents than had been previously believed. Kilcoyne et al. [20] 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. [9] reported to be at the top of the normal range for persons 16–19 years of age (males 135 mmHg; females 130 mmHg).

Similar 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 [21–24]. From these studies, the investigators detected initial rates of hypertension, when adult criteria were used, at approximately 5 %, and this rate decreased with repeat

blood pressure measurement. These reports also noted lower levels of blood pressure 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 [20, 21]. An effect of weight on blood pressure was also described [21, 24]. Together these reports emphasized a need to develop a better definition of hypertension in the young, which was based on reference data derived from a large sample of healthy children.

The gaps in understanding the normal distribution of blood pressure levels and hypertension in childhood was recognized by the National Heart, Lung, and Blood Institute which directed the National High Blood Pressure Education Program to appoint a Task Force on Blood Pressure Control in Children and Adolescents. The Task Force published its first report in 1977 [25]. 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 or "at-risk" blood pressure measurements. The blood pressure distribution curves 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 9,283 children from age 5 to 18 years, with an additional 306 children aged 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 were a substantial advancement, particularly for clinicians who care for children. Although based on cross-sectional data, the curves indicate a progressive increase in blood pressure level with age, a trend that is concurrent with an increase in 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 systolic and 90 mmHg diastolic pressure, with a progressive rise to 18 years, at which age the 95th percentile was over 150 mmHg systolic and at 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 that seemed to be high for older adolescents, particularly in view of 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. 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. What was not clear was whether the blood pressure curves published in the report were an accurate reflection of the normative blood pressure distribution in healthy children. The National Heart, Lung, and Blood Institute 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, blood pressure trend, and growth in

Table 10.2 Data sources for the Second Task Force Report

Source	Age (year)	N
Muscatine, IA [27–29]	5–19	4,208
University of South Carolina [30]	4–20	6,657
University of Texas, Houston [31]	3–17	2,922
Bogalusa, LA [32, 33]	1–20	16,442
Second National Health and Nutrition Examination Survey [34]	6–20	4,563
University of Texas, Dallas [35, 36]	13–19	24,792
University of Pittsburgh [37]	Newborn-5	1,554
Providence, RI [38]	Newborn-3	3,487
Brompton, England [39, 40]	Newborn-3	7,804

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 level 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 [26]. 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. Table 10.2 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 [27–40] 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 to 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 (and 90th) 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 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, the blood pressure values that approximated the 95–99th percentiles were designated significant hypertension, and the 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 publication of sixth report of the Joint National Commission in 1998 [10] that hypertension stage was introduced as method to guide in patient care and clinical management decisions in adults.

Subsequent to the 1987 Second Task Force Report, additional childhood blood pressure data were developed from the National Health and Nutrition Examination Survey III (NHANES) [41]. Reports were also published on data indicating that children with elevated blood pressure in childhood often developed hypertension in early adulthood [42]. Based on increasing support for the concept that the origins of hypertension began in the young, rationale was developing for 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, including preventive guidelines.

The addition of the new blood pressure data and reanalysis of the entire childhood database resulted in blood pressure distribution curves that were slightly lower but generally consistent with the findings of the Second Task Force [43]. The third report, 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 was considered in the analysis that was conducted by the Second Task Force, as well as the analysis 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 systolic and diastolic blood pressure level at the 90th and at the 95th percentile for each height percentile and each age from one through 17 years. These tables provided a better view on the variation of blood pressure according to height as well as age.

The childhood blood pressure data was reexamined by a Fourth Working Group that published expanded blood pressure percentile tables in 2004 [44]. 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 ≥95th percentile verified on repeated measurement. This report provides additional precision in the staging of hypertension. Stage 1 hypertension is systolic or diastolic blood pressure between the 95th percentile and 5 mmHg 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 is defined as systolic and/or diastolic blood pressure ≥90th percentile and <95th percentile. The definition of prehypertension in adults is systolic blood pressure between 120 and139 mmHg or diastolic blood pressure between 80 and 89 mmHg [14]. In adolescence, beginning at age 12 years, the 90th percentile is higher than 120/80 mmHg. Therefore, to be consistent with the adult definition of prehypertension, prehypertension in adolescents is defined as blood pressure from 120/80 mmHg to <95th percentile. In this report, additional guidelines were provided in evaluation and treatment according to prehypertension, stage 1 hypertension, and stage 2 hypertension in childhood. Recommendations were also given on evaluation for other risk factors related to high blood pressure and for target organ damage.

Following publication of the report of the Fourth Working Group, subsequent publications have reported data on the prevalence of hypertension based on these definitions. Hansen et al. [45] 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 ages 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 6,790 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 in adolescence was 15.7 % [46]. 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. [46], the prevalence 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 [47]. The association of overweight and obesity with higher blood pressure has been consistently demonstrated in children [45, 46, 48] as well as adults. The effect of the increase in childhood obesity on blood pressure was demonstrated by Muntner et al. [49] who compared blood pressure levels in children on data in two sequential NHANES. Their analysis identified a significant upward trend in blood pressure levels in children and adolescents. They 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 [50]. 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 [44] are based on child population data that were largely developed prior to the current child obesity epidemic. To determine if there is a substantial effect of obesity on that normative data Rosner et al. [51] reexamined the childhood blood pressure normative data by including only normal-weight children (BMI <85th percentile). They found that the blood pressure percentile levels were somewhat lower, but that the sex-, age-, and height-adjusted percentile levels published in the Fourth Working Group report were not substantially confounded by recent increases in the prevalence of childhood obesity. The blood pressure percentile tables based on age, sex, and height of normal-weight children are available in the publication and at http://sites.google.com/a/channing.harvard.edu/bernardrosner/pediatric-blood-press. The current criteria for high blood pressure in childhood provide important information on population trends in the prevalence of childhood hypertension.

Although the blood pressure levels in the tables are not markedly lower, the results of this analysis along with the known adverse effect of obesity on blood pressure in childhood do raise the question of whether the normative blood pressure data should be based on normal-weight children only.

The current blood pressure norms are based on data that has been developed from over 70,000 children and adolescents. It is the data that has been collected according to rigorous and quite uniform 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 this data and development of blood pressure norms provides 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 [52] and Asia [53]. 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 age, height, and body weight throughout childhood.

The quality of contemporary blood pressure normative data has improved compared to that provided in the first Task Force report published in 1976. This is largely due to application of a consistent methodology in blood pressure measurement. In addition to the childhood obesity epidemic, other changes in clinical practice need to be considered in the use of the normative blood pressure tables. The normative blood pressure data are based on blood pressure measurements obtained by auscultation. In clinical practice, there has been increasing reliance on blood pressure automated 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, and it is unlikely that child population data of similar magnitude will be developed on each of the available devices.

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 is 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 [54]. 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. Another area in which normative blood pressure in children is being developed utilizing instrumentation is ambulatory blood pressure monitoring (ABPM). ABPM has become an important tool in the clinical evaluation of high blood pressure in children and adolescents, as well as a clinical research procedure [55]. The development of normative childhood data on ABPM is especially challenging in data collection and data analysis. Despite these difficulties, normative ABPM data in children, with age- and sex-adjusted percentiles, are available [56].

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, and because it largely precedes the child obesity epidemic, these data provide a basis on which to detect trends in blood pressure level and prevalence of hypertension in children. It should be remembered that hypertension in childhood is based on a statistical definition. Therefore, in the absence of outcome data that connect a childhood blood pressure level with subsequent injury or events, the 95th percentile remains a working definition. What remains to be resolved is whether the 95th percentile adequately represents the risk for hypertension-related injury.

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Ambulatory Blood Pressure: Methodology and Norms in Children

11

E.M. Urbina

Abstract

Office BP readings taken as part of routine vital signs determination are subject to error especially if automated devices are used. Furthermore, office BP measures cannot rule out the "white-coat" effect (BP levels are normal outside of a medical setting though high in the office) or identify "masked" HTN (normal office but high out-of-office BP levels). To address these issues, ambulatory blood pressure monitoring (ABPM) has seen increasing use. Due to its superior accuracy in classifying BP levels, ABPM has also been shown to be cost-effective in the evaluation of childhood hypertension as compared to repeat office visits, and recent guidelines have given more consideration to routine use of ABPM. In this chapter, we will discuss the use and interpretation of ABPM.

Keywords

Hypertension • Ambulatory blood pressure monitoring • Pediatrics • Left ventricular hypertrophy • Target organ damage

Abbreviations

ABPM	Ambulatory blood pressure monitoring
BP	Blood pressure
cIMT	Carotid intima-media thickness
CKD	Chronic kidney disease
CV	Cardiovascular
GFR	Glomerular filtration rate
HTN	Hypertension
LVH	Left ventricular hypertrophy
LVMI	Left ventricular mass index
MAP	Mean arterial pressure
MH	Masked HTN
OSA	Obstructive sleep apnea
PWV	Pulse wave velocity
T1DM	Type 1 diabetes mellitus
TOD	Target organ damage
WCH	White-coat hypertension

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Prevalence of Childhood Hypertension

Although hypertension (HTN) is defined by blood pressure (BP) levels greater than or equal to the 95th percentile for healthy children, when replicate readings of BP are obtained, the prevalence of HTN in children and adolescents is less than 5 %. Historical studies suggested a prevalence of 1–2 %, but recent data such as a study from BP screenings conducted in Houston, TX, demonstrated a prevalence of HTN of just over 3 % [1], with an even higher prevalence of 4.5 % in obese children [2]. NHANES data have suggested the prevalence of HTN has now reached nearly 4 %, and the prevalence of prehypertension has now reached 10 % [3]. Unfortunately, minority children are more severely affected by these trends, similar to the trends seen in minority adults [4].

Utility of Ambulatory Blood Pressure Monitoring

Blood pressure is important to measure because BP levels reflect risk for target organ damage and future cardiovascular (CV) events. Autopsy studies such as the Bogalusa Heart Study and the Pathobiologic Determinants of Atherosclerosis in Youth study have clearly demonstrated histologic evidence of adverse vascular changes related to HTN in youth [5, 6]. Unfortunately, office BP readings when taken as part of routine vital signs determination [7] are subject to error, especially if automated devices are used [8]. Furthermore, office BP measures cannot rule out the "white-coat" effect (BP levels are normal outside of a medical setting though high in the office) or identify "masked" HTN (normal office but high out-of-office BP levels). The white-coat effect is extremely common in children [9], with a prevalence of near 40 % in many large pediatric studies [10, 11]. Although challenges to widespread implementation exist [12], ambulatory BP monitoring (ABPM) has seen increasing use since it can rule out masked or white-coat HTN, it eliminates observer bias, and it allows assessment of nocturnal BP, which has prognostic significance [13]. Due to its superior accuracy in classifying BP levels, ABPM has also been shown to be cost-effective in the evaluation of childhood HTN as compared to repeat office visits [11, 14] For these reasons, recent guidelines have given more consideration to routine use of ABPM [15].

Conditions Where ABPM May Prove Especially Useful

Secondary HTN: When HTN is detected in very young children or stage 2 HTN is found, ABPM may be useful in determining if secondary HTN is present (Table 11.1). Higher nocturnal SBP load and 24-h DBP load (see Table 11.2) should increase suspicion for a secondary cause. Presence of daytime DBP load >25 % and nocturnal SBP load >50 % had 92 % specificity for predicting secondary hypertension in one study [16]. Blunted nocturnal dipping (see Table 11.2) had 90 % specificity in predicting secondary HTN in another study from the Czech Republic [17].

ABPM is also useful in conditions where patients are at high risk for HTN including children with frequent urinary tract infections [18], Williams syndrome [19], Cushing syndrome [20], anorexia nervosa [21], chronic fatigue syndrome [22], polycystic ovary syndrome [23], and repaired coarctation of the aorta [24]. Subjects at genetic risk for HTN may also demonstrate higher ABPM levels [25], so it is no surprise that twin studies suggest heredity has a large impact on ABPM [26]. Children with a parental history of HTN also have higher ABPM than those without a history, while this genetic influence was not found for office BP [27]. In addition to genetics, early life events are also important. Children born after a pregnancy complicated by preeclampsia had significantly higher mean 24-h ABPM levels than normal controls [28]. Impaired fetal growth, regardless of the cause, has also been linked to higher ambulatory SBP at 12 years of age [29], and low

Table 11.1 Conditions where use of ABPM may improve patient care

Condition		Benefit
Secondary hypertension		Abnormalities in ABPM may indicate a greater likelihood for secondary HTN
Genetic risk for HTN		Patients with strong Fam Hx of HTN may demonstrate abnormalities
		Stiffer arteries predisposing to HTN are found in patients with Williams and Turner syndromes
		Renal artery stenosis may lead to HTN in neurofibromatosis 1
White-coat/masked HTN		Are conditions that can only be diagnosed by ABPM
Prehypertension		Confirmation of diagnosis allows for continuation of lifestyle and avoidance of drug therapy
Obesity		Obese subjects have a higher prevalence of white-coat and masked HTN especially if they have concomitant obstructive sleep apnea, polycystic ovary, or metabolic syndrome
Risk for target organ damage		If ABPM is abnormal, it may indicate a need for further imaging
Diabetes		Tighter BP control reduces risk for albuminuria
Solid organ transplant		Transplant recipients have higher prevalence of masked HTN and nocturnal HTN
Renal disease	Chronic renal insufficiency/transplant	Tighter 24-h BP control proven to delay progression of kidney disease and can prevent graft loss
	Renal scarring	Abnormal ABPM correlates with renal scarring

Table 11.2 Variables used in analysis of ABPM studies

Variable	Definition/calculation	Clinical or research
Mean BP	The average of readings for a given time period (24 h, awake period, sleep period)	Clinical
BP load	Percentage of readings above a threshold value (usually the 95th percentile)	Clinical
BP dipping	Percent decline in systolic or diastolic BP during sleep (calculated as mean awake BP – mean sleep BP/mean awake BP × 100 %)	Clinical
Morning surge	Difference between morning BP and sleep nadir	Research (clinical in adult ABPM)
BP variability	Standard deviation of the mean systolic or diastolic BP for a given time period (available from ABPM software)	Research
Hyperbaric index	Area under the curve above a preselected BP threshold	Research
Smoothness index	Average of the hourly BP reductions over 24 h/standard deviation of hourly BP reductions	Research
AASI	Ambulatory arterial stiffness index (1 – regression slope of DBP/SBP from 24-h ABPM)	Research

ABPM ambulatory blood pressure monitoring, *BP* blood pressure, *DBP* diastolic blood pressure, *SBP* systolic blood pressure

birth weight was associated with reduced nocturnal dipping in children [30].

ABPM can also be used to examine the effect of lifestyle and vasoactive substances on CV risk. In adolescents, higher 48-h and nighttime BP levels were found with sleep deprivation [31]. Psychosocial stress [32], higher salt intake [33], and caffeine also increase ABPM levels in children [34]. The circadian effect of stimulant medications used for attention deficit hyperactivity disorder on BP can also be more effectively evaluated with ABPM since these drugs are usually only dosed during school hours. One study found that total and waking DBP was 3–4 mmHg higher on active treatment, a magnitude that may be clinically relevant in the child with borderline BP levels [35].

White-coat HTN: White-coat HTN (WCH) can be diagnosed in the situation where a patient's office BP level is elevated (≥ the 95th percentile for age, gender, and height [36]) in the clinic, while ABPM averages are less than the 95th percentile [37]. Some investigators believe WCH represents a transient, stress-induced elevation of BP associated with office visits. WCH has been found to occur with greater frequency in obese youth [38] and in younger patients such that the prevalence decreases after age 12 [39]. WCH is also more commonly found in patients with borderline levels of office BP. The likelihood of WCH decreases if office BP is very much below the 90th percentile or above the 95th percentile [9, 40]. The exact prevalence of WCH is not known. Although one study of male athletes undergoing a pre-sports physical found the prevalence of WCH to be 88 %, the true prevalence is likely much smaller on the order of 30 % [41] to 40 % [11]. Nevertheless, these data suggest that up to a third of patients presenting for evaluation of pediatric HTN may in fact have WCH, a condition that can only be diagnosed with ABPM.

Although pediatric BP guidelines do not recommend drug therapy for WCH [42], it is still a condition that requires careful follow-up, as it may not be entirely benign. In adults, subjects with WCH may have evidence of mild cardiac [43] or vascular [44, 45] target organ damage (TOD) explaining the higher risk for CV events in adults with WCH [46]. Similarly, children with WCH were found to have higher left ventricular mass index (LVMI) than normotensive controls [38, 47]. One investigation found 1/3 of children with WCH actually had LV hypertrophy (LVH) as defined by an LVMI above the 95th percentile for age and sex [48]. Vascular abnormalities have also been reported, including abnormal reactive hyperemia in the middle cerebral artery [49] and increased carotid intima-media thickness (cIMT) in WCH compared to controls [50].

Masked HTN: Masked HTN (MH) is identified when BP levels in the office are normal but HTN is evident on ABPM. This is a difficult condition to diagnose as the practitioner must have a high enough index of suspicion to order an ABPM. A common scenario is when multiple other providers report hypertensive BP levels when measured under similar conditions. Another clue is the presence of obesity which increases the prevalence of this condition [51]. Furthermore, if TOD (i.e., LVH) is present despite normal clinic BP, MH should be ruled out. The prevalence of MH is not precisely known, but likely much lower than for WCH (Fig. 11.1). Estimates vary based on the population studied. In healthy children, the prevalence was reported to be 5.7 % [52] with a higher prevalence found in patients referred to a HTN clinic (9.4%) [38], in a clinic with patients with secondary HTN (15 %) [53] to 24 % in renal transplant recipients [54]. Unfortunately, compelling data link MH to CV risk [55] even more strongly than for WCH and MH has been implicated in progression of chronic kidney disease (CKD) in adults [56]. In youth, MH identifies patients who are more likely to progress to sustained office HTN [52] and who are more likely to demonstrate elevated LVM [38]. In fact, prevalence of LVH may be the same (around 20%) for adolescents with MH compared to patients with confirmed stage 1 hypertension [57]. Children with CKD seem very prone to demonstrate the MH pattern (38 %) with the odds ratio for LVH equal for MH and confirmed HTN (4.1 vs. 4.3) [58]. For this reason, aggressive management may be recommended by pediatric hypertension experts.

Prehypertension: ABPM application may be especially helpful in evaluating patients with borderline levels of office BP (within 20 % of the 95th percentile) [59] since they are more likely to have WCH or MH compared to patients with BP values well below the 90th percentile or well above the 95th percentile. One study of youth referred to a HTN clinic did find true prehypertension in 20.8 % of subjects [41], thus identifying patients in need of nondrug aggressive lifestyle intervention. However, even in cases where mean ABPM values are normal and not prehypertensive, increased BP variability may be identified and this pattern is associated with TOD in adults [60]. Few studies have examined the relationship between prehypertension and TOD; however, there are data suggesting that LVM (Fig. 11.2) [61, 62], cIMT [62], and arterial stiffness

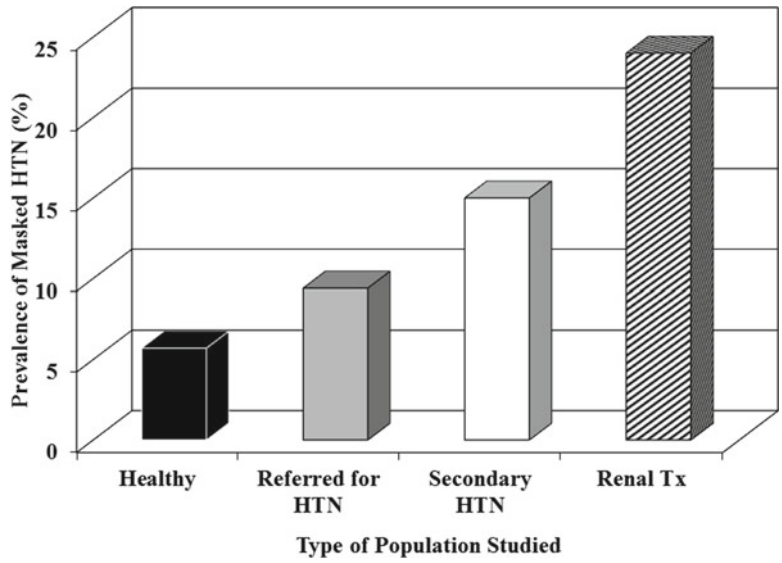

Fig. 11.1 Prevalence of masked HTN by clinical context (Adapted from healthy = Lurbe [52]; referred for HTN = Stabouli; [125] secondary HTN = Furusawa; [53] renal transplant = Paripovic [54])

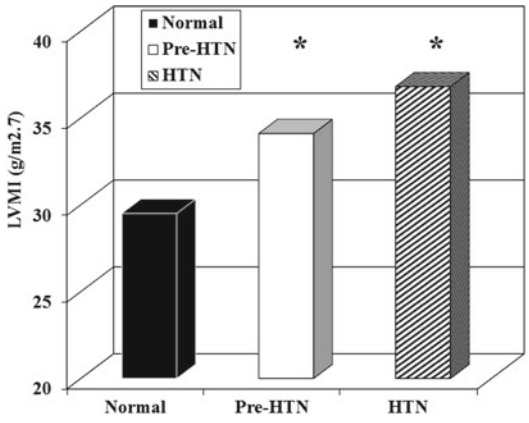

Fig. 11.2 Prehypertension on ABPM associated with higher LVM index. *$P < 0.01$ for LVM index in normotensive subjects < pre-HTN and HTN; $N = 124$, mean age 15 years (Adapted from Stabouli [61])

[62] may be higher in prehypertensive youth as compared to their normotensive counterparts. Thus identifying the prehypertensive pattern is important in management of these higher-risk patients.

ABPM and Obesity-Related CV Risk Factors: Youth with obesity and clustering of CV risk factors have a higher prevalence of TOD, and ABPM is helpful in stratifying this risk. Much data have been published linking obesity to higher mean BP measured with APBM [63]. Obese youth may also demonstrate abnormal ABPM patterns such as reduced dipping of BP at night [64] which may increase risk for MH [65]. Insulin resistance induced by the obese state has also been demonstrated to be a determinant of daytime DBP, even after adjustment for level of obesity [66]. Obese insulin-resistant children are also more prone to develop obstructive sleep apnea (OSA) and concomitant increases in higher mean ABPM [67], daytime BP variability, and reduced nocturnal dipping [68]. More severe cases of OSA, such as found in children with an apneic-hypopneic index >5, have even higher nocturnal BP levels than less severely affected patients [69], and they also tend to have a more pronounced early morning BP surge [70], an ABPM pattern associated with increased risk for adverse CV outcomes in adults [71].

ABPM and Risk for TOD: Since LVH is an independent predictor of adverse CV outcomes in adults [72], echocardiography has emerged as the most utilized method to assess TOD in youth with HTN [42]. However, echocardiography is expensive, so accurate measurement of BP to determine which patients to refer for imaging studies is important. Fortunately, ABPM relates more strongly to LVM [73] in both hypertensive

and normotensive adults [74]. Most pediatric studies have demonstrated a relationship between ABPM levels and LVM [75, 76] with a linear increase in LVM seen in one study with increasing nighttime SBP [73]. BP load, a measure of severity of BP variability, has also emerged as an ABPM parameter that relates importantly to heart thickness [75]. Similarly, higher standard deviation score, another variability measure, also increased the odds ratio of having increased LVM index by 54 % [76]. Paradoxically, one multicenter study of children referred to a HTN clinic did not find an association between BP load and LVM [77]. Clearly, more research to delineate the utility of ABPM in predicting LVH in children is needed.

CV risk factor-related increases in cIMT are associated with adverse outcomes in adults including stroke and myocardial infarction [78]. Not surprisingly, increased cIMT is also associated with adverse levels of ambulatory BP [79]. The observation that this association persists after adjusting for office BP [80] suggests that ABPM provides incremental information above and beyond risk stratification provided by interpretation of office BP levels. Pediatric studies demonstrate a similar finding of thicker cIMT in hypertensive children with a significant correlation between cIMT and daytime SBP index ($r=0.47$; $p=0.003$) but not office BP [81]. Obesity influences both BP and IMT. In one study, obese youth had a significantly higher mean ABPM compared to the lean, and they demonstrated an increased cIMT despite the fact that only one-quarter were actually hypertensive [38]. Another group of investigators did not find a difference in cIMT between lean and obese subjects [82]; however, the obese children did have higher mean ABPM, and this was associated with higher carotid stiffness and lower endothelial function measured by brachial flow-mediated dilation [82]. Arterial stiffness can also be measured by non-ultrasound methods, including pulse wave velocity (PWV). In healthy school children, PWV was correlated with BP, but after adjustment for age, gender, and BMI, the difference in PWV between normo- and hypertensive youth was only significant when HTN was diagnosed with ABPM [83].

In adults, HTN-related renal damage, including increased rates of microalbuminuria, is more closely related to ambulatory rather than office BP levels [84]. Although no direct relationship was found between ABPM and creatinine clearance or albumin excretion rate in one study of children with HTN [73], another did show correlation between nighttime SBP and creatinine clearance in African-American subjects [85]. More recent data from an Italian cohort found children with prehypertension and high BP loads (percentage of readings above the 95th percentile) had lower glomerular filtration rate (79.15 vs. 96.78 ml/min/1.73 m [2] $p<0.006$) and higher protein excretion (198.29 vs. 118.31 mg/m [2]/day, $p<0.036$) compared to patients with normal BP loads [86], suggesting that ABPM may be useful in identifying young patients with borderline office BP levels that are at increased risk for BP-related renal decline.

ABPM in High-Risk Conditions: Many chronic pediatric medical conditions increase the risk for HTN-related target organ damage. In one study of children with type 1 diabetes mellitus (T1DM) age 14 ± 3 years, office BP correctly identified HTN in only 6 % of patients, while ABPM found abnormalities in 52 %, including nocturnal, white-coat, or masked HTN, conditions that can only be diagnosed with ABPM [87]. Many investigators hypothesize that poor diabetic control may be a factor in the development of HTN as HbA1c correlates with abnormal mean ambulatory SBP [88] and reduced BP dipping [89]. Identifying abnormal ABPM patterns in youth with T1DM is especially relevant because nocturnal HTN predicts higher cIMT [13], while higher diastolic BP load [90] and blunted nocturnal dipping [91, 92] are often found in patients with microalbuminuria. Reduced dipping has also been demonstrated in youth with type 2 diabetes mellitus [93] and even uncomplicated obesity [94] suggesting that ABPM can predict target organ damage in obese patients well before they progress onto full type 2 diabetes mellitus.

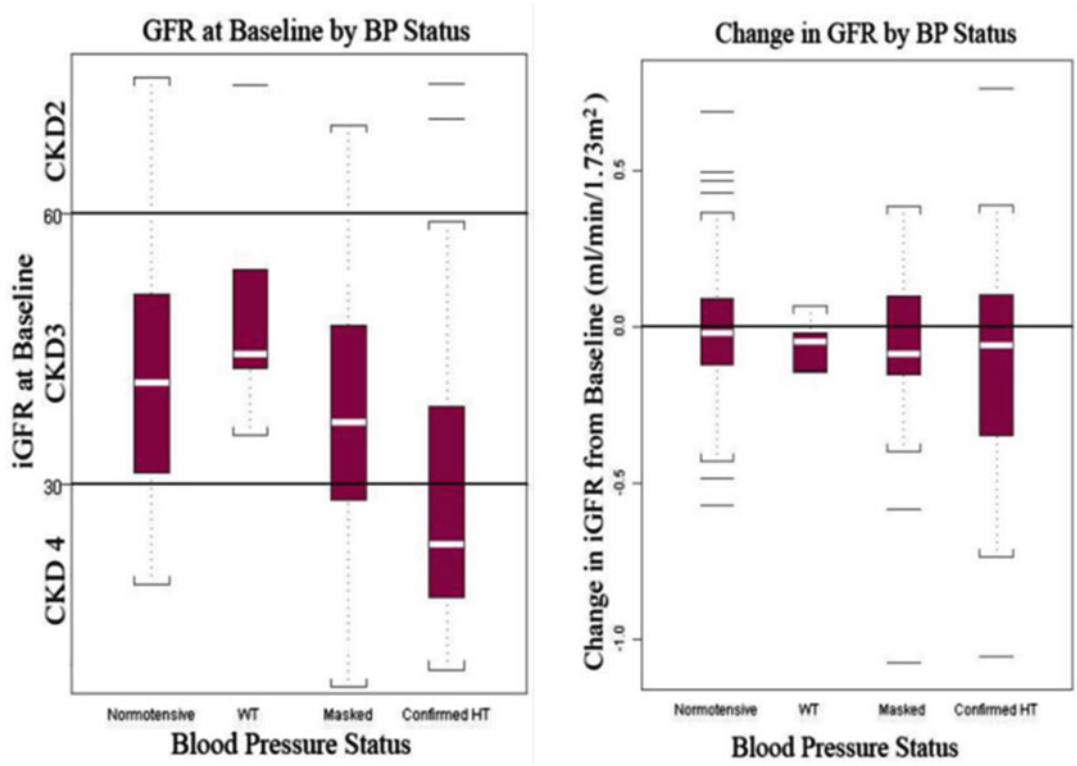

Fig. 11.3 GFR at baseline and change in GFR by blood pressure classification in the CKiD Cohort Study (Reproduced by permission [96])

CKD of childhood onset is recognized as a significant risk factor for adverse CV events in adults [95]. Unfortunately, children with CKD may have a higher prevalence of MH [58]. Furthermore, data from the Chronic Kidney Disease in Children study suggests that children with MH have lower glomerular filtration rate (GFR) at baseline with more rapid decline in GFR during follow-up compared to normotensive patients (Fig. 11.3) [96]. Fortunately, intensive BP control using ABPM has been proven to lead to slower progression of CKD [97]. For this reason, many pediatric nephrologists are using ABPM routinely [98, 99].

HTN is also very common after solid organ transplantation, likely related to immunosuppressive agents [100]. However, these patients often exhibit only nocturnal HTN which cannot be diagnosed with office BP measurement [101]. Even with good BP control in the office, inadequate 24-h BP control may be present [102] prompting BP drug therapy changes in many patients once ABPM patterns are recorded [103]. ABPM parameters, especially in pediatric kidney transplant recipients, are strongly related to both LVM [104] and carotid IMT [105]. For this reason, ABPM is used with increasing frequency to rule out target organ damage in these high-risk children.

Measurement and Interpretation of ABPM

The American Heart Association published detailed methods for performance and interpretation of ABPM studies in children and adolescents in 2008 [106] which were later adopted by European groups [15]. Selection of appropriate equipment is an essential first step. Few devices have undergone rigorous validation testing [107] in children, and none has received an unequivocal recommendation from the dabl Educational

Trust, an international consortium that reviews validation experiments for BP devices (http://www.dableducational.org/sphygmomanometers/p_devices_3_abpm.html, last accessed January 4, 2013). Practitioners also need to understand that auscultatory and oscillometric devices do not provide equivalent mean values for systolic and diastolic BP. Auscultatory devices evaluate Korotkoff sounds, while oscillometric devices measure mean arterial pressure (MAP) and calculate systolic and diastolic BP. Although auscultatory ABPM devices may provide mean levels more closely related to the gold standard of mercury sphygmomanometers, there are no large-scale studies of ambulatory BP using auscultatory devices. Therefore, most pediatric BP experts use the oscillometric device with the largest amount of normative data [37].

Once a device has been selected, it should be applied to the patient with an appropriate size BP cuff. BP is usually measured every 20 min during the day and every 30 min at night. Patients are instructed to record sleep and wake times and any unusual activity. Some investigators use fixed time periods (e.g., 08:00–22:00 for wake and 24:00–06:00 for sleep); however, this was shown to lead significant misclassification. Therefore, the use of patient-supplied time periods is recommended [108]. For a full-day record, at least one valid reading per hour is necessary [106]. The manufacturer's software can be programmed to edit out biologically implausible readings (SBP >240 mmHg or <70, DBP >140 or <40 mmHg, heart rate >125/min, pulse pressure <40 or >100mmHg or where DBP<SBP) [109]. These settings can be modified if performing ABPM in very young children [106].

Once the sleep and wake times are defined and erroneous readings removed from the record, the 24-h, wake and sleep mean BPs and BP load are calculated (for definitions, see Table 11.2). More advanced measures such as morning BP surge have not found routine use in pediatrics, although in adult studies, the surge correlates with stroke risk independent of mean and nocturnal ABPM [71]. Measures of BP variability are predominantly research tools with the standard deviation or coefficient of variance [110] for daytime or nighttime

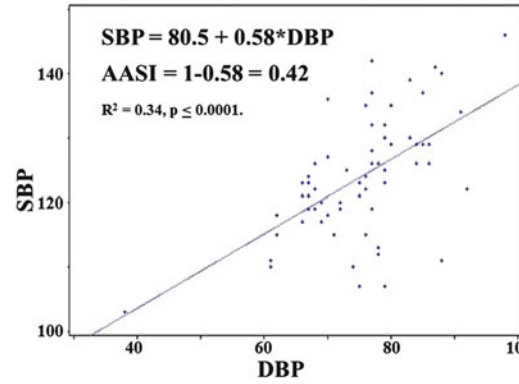

Fig. 11.4 Calculation of ambulatory arterial stiffness index (Reproduced by permission [96])

readings associated with target organ damage and CV mortality in adults [71]. Using fast Fourier analyses, reduced BP variability was found in children with more advanced CKD including lower glomerular filtration rate and higher levels of albuminuria [111]. Other advanced measures such as the hyperbaric index [112] and smoothness index, a measure of 24-h BP control [71], have only been utilized in adult studies. However, one study did measure ambulatory arterial stiffness index [71] (Fig. 11.4) in youth with HTN and found it was related to more traditional measures of arterial stiffness such as pulse wave velocity [113].

Normal Values: The most commonly used pediatric reference standards include data on over 1000 healthy children and adolescents collected in Germany [37, 114]. These data were presented in a tabular form in the 2008 AHA statement, stratified by sex and organized by height, a major determinant of BP levels [106]. For children less than 120 cm tall, it may be necessary to use tables by age which do go down to 5 years.

Despite the widespread use of these data to define "normal" ABPM levels, many limitations to the dataset are recognized [12]. First, only Caucasian children were included. Since many studies, such as the Bogalusa Heart Study, have demonstrated racial differences in resting BP [115] and at least one small study suggests racial differences exist in ambulatory levels [116], it is not clear if these all Caucasian cut points can be

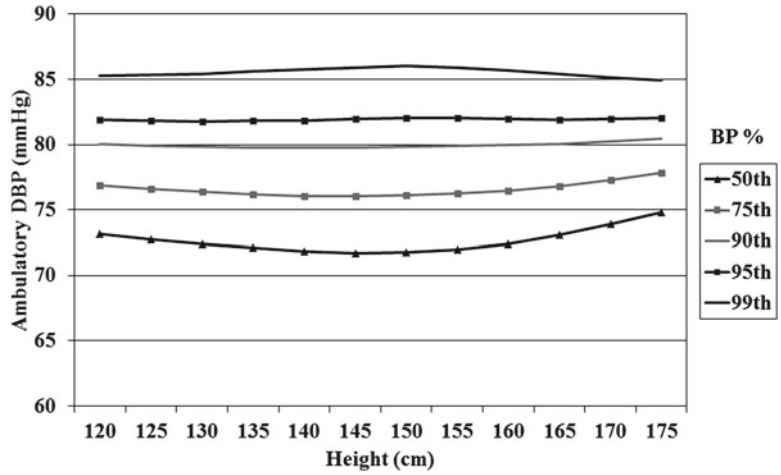

Fig. 11.5 Graph of mean daytime diastolic ambulatory BP for girls according to height (Adapted from Wuhl [37]. _ ENREF_114 (endnote reference 114))

used for children of diverse ethnic backgrounds. Another major concern with the German ambulatory BP data is the flat slope of diastolic BP across height (Fig. 11.5) [37, 114]. Some researchers speculate this represents a systematic error in the algorithm used to measure diastolic BP as resting mercury measures of diastolic BP do increase across body size in children and adolescents. Finally, there were relatively few children of short stature in the study, making it less useful for defining normal levels in smaller children. This is a major concern as children with CKD, who are at high risk for both hypertension and future CV disease, often manifest impaired linear growth. Despite these many limitations, until more extensive normative data across race/ethnicity, age, and body size are collected, the German data should be used in most situations.

Classification of BP Levels: The AHA statement recommends that a practitioner first needs to classify the resting office systolic BP (preferably measured with an auscultatory technique) using the tables in the Fourth Report [36]. Then the ABPM result should be examined to determine if the patient has ambulatory systolic normotension, hypertension, white-coat, or masked hypertension [106, 117].

However, there is controversy among pediatric HTN experts whether this classification scheme truly captures risk of TOD due to elevated BP levels. For this reason, many pediatric HTN experts advocate for a more comprehensive classification scheme (Table 11.3) [96]. For instance, the AHA statement gives no recommendation on how to classify young patients with isolated ambulatory diastolic HTN. This is particularly disturbing because diastolic HTN on ABPM may be one of the strongest indicators that secondary causes of HTN may exist [16]. For this reason, some practitioners classify subjects based on either their systolic or diastolic ambulatory levels. Another method to avoid this issue would be to classify based on MAP. This approach is attractive because oscillometric devices measure MAP directly, so one could avoid the uncertainty with calculation of systolic and diastolic BP based on the different proprietary algorithms that each of the devices employ. Furthermore, the ESCAPE trial [97], a study designed to evaluate the benefit of aggressive versus traditional BP targets in preventing progression of CKD, found that treatment guided by ambulatory MAP can be successfully applied in a large multicenter trial. Before this can be implemented for a wider group of patients, more studies assessing the usefulness of ambulatory MAP will need to be performed.

Another challenge in interpreting ABPM is how to classify patients if they only demonstrate nocturnal HTN and their 24-h mean levels are

Table 11.3 Suggested revised schema for staging of ambulatory BP levels in children (Adapted from Ref. [96] with permission)

Classification	Office BP[a]	Mean ambulatory SBP or DBP[b, c]	SBP or DBP load[c]
Normal BP	<90th percentile	<95th percentile	<25 %
White-coat HTN	>95th percentile	<95th percentile	<25 %
Masked HTN	<95th percentile	>95th percentile	>25 %
Pre-HTN	≥90th percentile and <95th percentile	<95th percentile	25–50 %
Ambulatory HTN	>95th percentile	>95th percentile	25–50 %
Severe ambulatory HTN (at risk for end-organ damage)	>95th percentile	>95th percentile	>50 %

[a]Based on the National High Blood Pressure Education Program Task Force Standards [36]
[b]Based on ABPM values of Soergel et al. or the smoothed values of Wuhl [37, 114]
[c]For either the wake or sleep period of the study, or both

normal. Certain patient groups, such as those with CKD and diabetes and patients after solid organ transplantation, may have a higher prevalence of nocturnal HTN [101] which may have prognostic implications. Therefore, isolated abnormalities of sleep BP on ABPM should prompt further evaluation and management.

Another ambulatory BP parameter poorly addressed in the AHA statement is elevated BP load. The investigators in the Chronic Kidney Disease in Children study felt there was enough evidence linking this pattern of spiking BP with normal mean levels to TOD that they decided to classify these patients as having masked HTN [58]. Whether this approach should be extended to other patient populations is not clear. However, children with elevated load should certainly be followed closely especially if resting office BP levels are in the prehypertensive range.

Conclusions

ABPM is now well established as a useful clinical tool in the evaluation of the pediatric patient presenting for evaluation of suspected HTN. Due to the high prevalence of white-coat HTN, initial ABPM has been estimated to produce a net savings over $2.4 million per 1,000 children [11]. Furthermore, HTN treatment guided by ABPM was shown to prevent progression of carotid IMT in renal transplant recipients [105] and was associated with regression of carotid IMT and LVM in adolescents with primary HTN [118]. ABPM measures also maintain relative rank (tracking) better than office readings over a 15-year period [119], and ABPM results have less variability than office BP readings. The ability of ABPM to better approximate a subject's true BP level may allow reduction of sample size by up to 75 % in antihypertensive drug efficacy studies [120].

There are gaps in the knowledge base, however. More validation experiments need to be conducted in children with a variety of ABPM devices, and comparisons between auscultatory and oscillometric devices need to be made in terms of utility, ease of use, and normal mean values. Age-related differences between casual and ambulatory BP measures need to be defined further [121]. Normative data across different ethnicities are also lacking. This is especially important as many studies have demonstrated difference prevalence for HTN depending whether casual [122, 123] or ambulatory data [124] were employed to set normal cut points. Correlations between BP variability and target organ damage in youth with HTN should also be sought, and more data on the usefulness of circadian BP control are needed.

Current guidelines for use of ABPM are also insufficient. There is clear evidence for the benefit of performing ABPM in children suspected of being hypertensive, but no hard indications are given [106]. The AHA ABPM statement also does not provide clinicians with recommendations on patient management after ABPM has

been performed [106]. For instance, there is risk for target organ damage with white-coat and masked hypertension and prehypertension (as outlined above), yet no consensus has been reached as to whether these conditions mandate drug therapy to lower blood pressure. Hopefully, the recommendations for use of ABPM in children will be strengthened based upon recently published studies. Despite these limitations, ABPM will see increasing use in pediatric patients. Since intensive BP control only achievable with ABPM has already proven effective in reducing the prevalence of LVH [10] and progression to end-stage renal disease in children [97], it is clear that consistent application of ABPM will assist clinicians in improving BP control and reduce the burden of CV risk in children and adolescents with hypertension.

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Epidemiology of Essential Hypertension in Children

12

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Abstract

Essential (primary) hypertension is detectable in children and adolescents and, as in adults, is associated with a positive family history of hypertension, obesity, and lifestyle factors. Blood pressure (BP) levels and the prevalence of hypertension in children and adolescents have increased, largely due to the childhood obesity epidemic. The prevalence of primary hypertension in childhood is estimated to be approximately 3.5 %, and the prevalence of prehypertension in childhood is approximately 3.5 % with higher rates among adolescents. Although adverse outcomes of death and cardiovascular disability are rare in hypertensive children, intermediate markers of target organ damage such as left ventricular hypertrophy, thickening of carotid vessel wall, retinal vascular changes, and subtle cognitive changes are detectable in children and adolescents with high BP. Considering the rates of verified hypertension in asymptomatic children and adolescents, high BP is a common chronic health problem in childhood.

Keywords

Blood pressure • Hypertension • Prehypertension • Childhood • Adolescence

Introduction

Hypertension affects over one billion persons and is the leading cause of premature death among adults throughout the world, including both developed, developing, and lesser developed countries [1]. Essential (primary) hypertension emerges from a complex interplay of genetic, environmental, and behavioral factors. Due to the hereditary component of hypertension, the disorder is considered to have its origins in the young [2]. Although generally considered a disorder limited to older adults, hypertension is detectable in children and adolescents and is not uncommon. Population changes in health-related behaviors, including the childhood obesity epidemic, indicate that the rates of hypertension in the young are increasing [3]. Several challenges regarding hypertension now confront clinicians

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who care for children and adolescents including detecting hypertension, distinguishing secondary hypertension from primary hypertension, evaluating patients for hypertension-related risk factors and target organ damage, applying interventions to control BP, and encouraging preventive lifestyles. This chapter discusses the epidemiology and current knowledge on the development of primary hypertension in children and adolescents.

Definition of Hypertension and Prehypertension in Childhood

The definition of hypertension in adults is based on the approximate level of BP that marks an increase in cardiovascular events and mortality. Several expert panels have defined adult hypertension as systolic pressure [3] 140 mmHg or diastolic pressure [3] 90 mmHg [1, 4]. These numbers represent the approximate BP levels above which the risks for morbid events are significantly heightened and the benefits of treatment are established. It is also recognized that the risk for cardiovascular events attributable to BP level in adults does not begin at 140/90 mmHg but is linear with an increase in risk beginning at BP levels below 140/90 mmHg. For BP levels greater than 115/75 mmHg, the risk for hypertension-related events doubles with each 20 mmHg increase in systolic pressure or each 10 mmHg increase in diastolic BP [5]. Based on these findings in adults, prehypertension is defined in adults as systolic BP between 120 and 139 mmHg or diastolic BP between 80 and 89 mmHg, and lifestyle changes are recommended to prevent or delay progression to hypertension [1].

Outcome data on hypertension-associated events, including stroke, heart failure, kidney failure, and death, support the definition of hypertension in adults. Similar data to define hypertension in childhood, based on risk for events in later years, are not available. Master et al. [6] published a report in 1950 which proposed that a BP level that was two standard deviations beyond the statistical mean, or greater than the 95th percentile, should be considered abnormal. Using a statistical method to define the normal range of BP, they described the normal range of systolic BP in males to be 105–135 at 16 years of age and subsequently rising progressively with age. This statistical definition of hypertension has been dismissed in adults due to the outcome data that demonstrate the risk for adverse events increases well below the 95th percentile in adults. However, Master's report was the earliest to show that the normal range of BP is lower in persons aged 16–19 years compared to early adulthood, and gender differences were also identified. Of most significance is that it provided a statistical method to define the normal BP range, and abnormal BP could be defined in the absence of mortality or morbidity end points.

Early efforts to describe the normal BP range according to age throughout childhood reported markedly different findings [7]. In a recent analysis, Din-Dzietham et al. [8] applied the 95th percentile definition of high BP, based on the most current BP percentile tables published in 2004 [2], to data from the early child BP surveys. As shown in their report, in using the current BP level for the 95th percentile (by age and sex), the rates of high BP in the earlier surveys were astonishingly high. According to current BP levels for the 95th percentile, the overall estimated prevalence of high BP among children in the 1963–1970 survey would be 37.2 %, in the 1971–1975 survey it decreased to 16.9 %, and in the 1976–1980 it decreased to 11.1 %. By 1982–1984 the prevalence was 4.7 %, and the lowest was 2.7 % in the 1988–1994 survey. The earliest childhood BP surveys were, in general, based on a single BP measurement, and a standardized BP measurement methodology was not uniformly applied. It is unlikely that the prevalence of high BP was so high in 1963 and that the prevalence would change so drastically from 1963 to 1994. What changed is the body of normative BP data from which the BP percentiles were derived [9]. Subsequently, BP data were obtained on healthy populations of children that applied standardized methods of BP measurement and included growth and development measurements. This collective body of child BP data provided the BP distribution data for the Second Task Force Report on Blood Pressure in Children and Adolescents [10]. Subsequently, there has been

little shift in the child BP distribution [11], until the recent upward trend attributed to the rising rates of childhood obesity [3, 8].

Rather than a single BP level, the top portion of the age-, sex-, and height-specific BP distribution continues to be used to define high BP throughout childhood. Hypertension in childhood is defined as systolic and/or diastolic BP that is ≥95th percentile for age, sex, and height. Previously, the term "high normal" was applied to children with BP levels ≥90th percentile but <95th percentile. To be consistent with adult terms, and the concept that BP risks are linear rather than categorical, this term has been changed to prehypertension. Therefore, prehypertension is defined as systolic and/or diastolic BP that is >90th percentile (for age, sex, and height) but <95th percentile. However, this designation remains arbitrary and without supportive childhood evidence. Moreover, in adolescence, the 90th percentile is often higher than the adult threshold for prehypertension of 120/80 mmHg. Therefore, beginning at age 12 years, prehypertension is defined as BP levels in the range from 120/80 mmHg to the 95th percentile. The rationale for this definition is based on the findings that the risk for events in adults begins to rise at a BP level above 115/75 mmHg and for clinical purposes adolescents could benefit from preventive lifestyle interventions as well as adults. BP levels that are consistently above the 95th percentile are staged for severity. Stage 1 hypertension is defined as an average BP level from the 95th percentile to 5 mmHg above the 99th percentile. Stage 2 hypertension is defined as an average BP that exceeds 5 mmHg above the 99th percentile. Due to BP variability within individual patients, in clinical practice the diagnosis of hypertension and prehypertension requires repeated measurements [2]. In adults the diagnosis of hypertension is verified by BP ≥140/90 mmHg on two separate visits. To avoid overdiagnosis of hypertension in a child with a single elevated BP, three separate visits for BP measurement are recommended, with an average BP ≥95th percentile required for diagnosis of hypertension. An exception to the necessity for repeated BP measurement would be stage 2 hypertension or a child with symptomatic hypertension.

In other countries the BP percentile levels used to define high BP in children vary somewhat from the US definitions described above. High BP in the United Kingdom is defined as BP above the 98th percentile for age [12]. BP reference values have also been reported in Northern Europe [13] and Asia [14]. These reports describe a slightly higher BP level at the 95th percentile. However, all epidemiologic reports on normative childhood BP data demonstrate a consistent and significant relationship of BP with age, height, and body weight throughout childhood.

Prevalence of Childhood Hypertension

The prevalence of pediatric hypertension worldwide is not known due to regional differences in the definition of high BP, the distribution of reference BP data, and the BP measurement methodology. Based on the use of ≥95th percentile to define hypertension, it would be expected that the prevalence of hypertension would be approximately 5 %. However, due effects of accommodation and regression to the mean with repeated measures, the prevalence of hypertension is lower than 5 % and had been expected to be from 1 to 3 % following the recommended three separate measurements on children with an initial BP measurement ≥95th percentile.

Recent reports provide a more precise estimate of the prevalence on hypertension verified by separate measurements. Hansen et al. [15] applied the above criteria for hypertension and prehypertension to electronic medical record data from well-child care visits in over 14,000 healthy asymptomatic primary care patients. With the advantage of data on repeated BP 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 6,790 high school students (11–17 years). Using the recommended repeated BP

measurements on those with an elevated initial BP measurement, among adolescents the prevalence of hypertension was 3.2 % and the prevalence of prehypertension was 15.7 %. In this study the prehypertension designation was based on from one to three separate BP measurement sessions [16]. In both reports the presence of obesity was associated with higher rates of high BP. In the study on high school students by McNeice et al. [16], the prevalence of hypertension and prehypertension combined was over 30 % in obese boys and from 23 to 30 % in obese girls depending on ethnicity.

The childhood obesity epidemic [17] and the strong relationship of BP with body weight indicate that the population prevalence of high BP in the young will be increasing. The epidemiologic evidence to support an adverse impact of childhood obesity on child BP levels has been questioned because, as discussed previously, the earlier population data on child BP (from 1963 to 1984) described considerably higher BP values relative to data obtained after 1984 [18]. When the entirety of the child BP survey data from 1963 to 1994 is compared, it would appear that child BP levels are decreasing despite an increase in child obesity within the last decade. However, the variable methods used in the earlier BP surveys limit the ability to define a longitudinal trend in child BP over several decades. An analysis that examined changes in BP level and prevalence of hypertension throughout childhood from two more recent sequential national cross-sectional National Health and Nutrition Examination Surveys (NHANES) studies identified a significant increase in both systolic and diastolic BP. The BP increase is most striking among minority groups that also have the highest rates of childhood obesity [3]. 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 [8]. Both analyses verified that the population increase in BP among children and adolescents is largely due to the increase in obesity prevalence. However, a recent report on population changes in BP among children 9–11 years of age in the United Kingdom from 1980 to 2008 described an increase in systolic BP over the time period but determined that the increase in BP was not explained by an increase in obesity. The preponderance of evidence indicates that obesity in childhood is strongly associated with higher BP. Other factors may have effects on BP that are additive or synergistic with obesity.

Blood Pressure Trends from Childhood to Adulthood

Despite the 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 portions of the distribution curve tend to maintain that position over time which is indicative of BP tracking [19]. For example, a community study of 1,505 children aged 5–14 years detected tracking of systolic and diastolic BP over a period of 15 years, with statistically significant correlation coefficients between child BP and later BP levels. Of 116 young adult participants who developed hypertension, 48 and 41 % had elevated childhood systolic and diastolic BP, respectively [20]. The patterns may vary by race but weight does not seem to significantly affect population tracking data [21, 22].

A recent systematic review and analysis of 50 prospective cohort studies by Chen and Wang [23] demonstrated significant BP tracking correlation coefficients from childhood into adulthood. The strength of the tracking increased with baseline age and decreased with length of follow-up. Their analysis of data from diverse populations demonstrated an overall average tracking coefficient of 0.38 for systolic BP. These findings confirmed the observation that higher BP levels in childhood are associated with higher BP levels in young adulthood. In another study, Sun et al. [24] examined serial data on participants in the Fels Longitudinal Study and derived age- and gender-specific BP levels in childhood that predicted hypertension in adulthood. Using random-effects models, they found that the earliest significant difference in childhood systolic BP values among adults with and without

hypertension occurred at age 5 years for males and 8 years for females. The interesting finding from this study is the level of childhood BP that was predictive of subsequent adult hypertension. The age- and gender-specific values for childhood systolic BP among adults with hypertension were below the 50th percentile for systolic BP in children of median height based on data in the *Fourth Report on Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents* [2]. Therefore, the childhood systolic BP values in the Fels Longitudinal Study that were predictive of future adult hypertension were well below childhood BP levels that are presently considered to be high risk. These results raise the question of whether the 95th percentile or the 90th percentile for BP in childhood adequately captures high-risk BP.

Incidence of Hypertension in Childhood

Among adults, the prevalence of hypertension increases with age, indicating that new cases of adult hypertension are diagnosed each year. Although primary hypertension is more commonly identified in adolescence than earlier in childhood, there is little information about the annual incidence of newly diagnosed children with hypertension. Within the National Childhood Blood Pressure database, a segment of adolescents had BP measurements at intervals of 2 and 4 years. An analysis of this data found that among adolescents with prehypertension, 14 % had hypertension 2 years later, yielding an approximate incidence rate of 7 % per year. A limitation of this data is that it is based on only a single blood pressure measurement for BP classification. Despite this limitation, the serial data indicate that those with high BP continue to have high BP. Among adolescents with high-risk BP values including those designated, from a single measurement, as having prehypertension and hypertension combined, 68 % of boys and 43 % of girls had prehypertension or hypertension 2 years later [25]. A rate for progression from prehypertension to hypertension, confirmed by average systolic or diastolic BP levels ≥95th percentile on three separate occasions, is considerably lower, as described by Redwine et al. [26]. These authors conducted a retrospective analysis of data from their Houston-based school screening program and detected an overall incidence of 0.7 % per year in a sample of 1,006 adolescents with a mean follow-up time of 2.1 years. Adolescents who were initially normotensive at initial screening developed hypertension at a rate of 0.3 % per year. The annual incidence of hypertension increased to 1.1 % among the adolescents who had prehypertension at initial screening. Adolescents with the highest incidence of hypertension occurred among adolescents with elevated BP measurements at all three screening visits. These adolescents developed hypertension at the rate of 6.6 % per year. These observations indicate that the adolescents with average BP levels that are consistently high are at the greatest risk for progression to hypertension.

Although the rates of progression from prehypertension to hypertension in adolescents appear to be low, the population impact of these rates is considerable. As estimated by Redwine and Daniels [27], assuming an annual incidence rate of 0.7 % among the current US adolescent population of 17,000,000 (www.census.gov), approximately 119,000 adolescents will develop hypertension over the next year, and more than half a million adolescents and young adults will be diagnosed with hypertension within 5 years. These numbers are not trivial and represent a significant health burden in premature cardiovascular and renal disease.

Risk Factors for Primary Hypertension in Childhood

Adult patients with primary hypertension commonly have a strong family history of hypertension along with a family history of cardiovascular diseases associated with hypertension. Similarly, children with primary hypertension frequently have hypertensive parents and grandparents. Primary hypertension is considered to have a major hereditary basis. However, contemporary large genetic epidemiology studies have not identified genotypic

patterns directly linked with primary hypertension. It is unlikely that changes in genetic background contribute to the recent increase in childhood BP levels [28]. Other environmental and behavioral factors are known to have an impact on BP level and progression to hypertension. Unlike genetic factors which are relatively stable, environmental factors including the food supply, dietary, and other lifestyle patterns do change. These factors are potentially modifiable and represent pathways to prevent or attenuate the hypertensive process.

A consequence of changing environmental factors is the childhood obesity epidemic. The prevalence of childhood obesity has risen to 16.9 % in US children and adolescents, and the prevalence of overweight and obesity combined is now 31.8 % [17]. Obesity is the risk factor most consistently associated with high BP in childhood [3, 15, 16, 29, 30], and the effect of obesity on BP level is detectable in children as young as 2–4 years of age [30]. The effect of excess body fat in childhood is not limited to children who are clinically obese, defined as body mass index (BMI) exceeding the 95th percentile. Overweight is defined as the BMI 85th to <95th percentile. Tu et al. [31] demonstrated that as childhood BMI exceeds the 85th percentile, the risk for high BP, including both prehypertension and hypertension, increases approximately fourfold. Childhood obesity is a strong predictor of adult obesity and obesity-associated morbidities. An analysis of data from four prospective cohort studies detected evidence that the consequences of childhood obesity may be reversible. From longitudinal data on over 6,000 subjects who were examined from childhood into adulthood, the authors found that subjects who were overweight or obese both as children and as adults had greater risk for metabolic and cardiovascular disease including hypertension. However, subjects who were overweight or obese as children and became non-obese by adulthood had risks for these outcomes that were similar to subjects who were never obese [32]. There are both population and clinical evidence on the BP benefits of effective interventions to reverse and prevent childhood obesity.

The usual dietary intake of sodium among children, as well as adults, in the United States and other westernized countries is high and exceeds nutritional requirements. The high sodium intake is primarily due to secular changes in the food supply and dietary patterns that involve increasing consumption of processed foods. According to current estimates, approximately 75 % of dietary sodium consumption is derived from processed food products or restaurant foods [33]. Among hypertensive adults, there is evidence to support the benefits of lowering sodium intake. The association of sodium intake with BP in children has been more difficult to define. He et al. [34] performed a meta-analysis on reported studies conducted between 1981 and 2004 that examined the effect of dietary sodium reduction on BP in children and adolescents. Their analysis of data from ten separate studies determined that a 54 % reduction in sodium intake was associated with a modest (2.47 mmHg) but significant reduction in systolic BP. The absolute reduction in BP associated with sodium reduction may seem small for an individual patient. However, the population effects are likely to be greater, especially considering the burden of sodium intake on BP that would be carried over a lifetime. Early studies by Rocchini et al. [35] measured BP response to sodium intake in obese adolescents before and following weight reduction. Among the obese adolescents who decreased adiposity through weight loss, there was a reduction in their BP sensitivity to sodium intake. The investigators concluded that obesity-associated hyperinsulinemia or heightened sympathetic nervous system activity associated with obesity could mediate the BP sensitivity to sodium in obese adolescents. This concept was addressed in an analysis of NHANES 2003–2008 data by Yang et al. [36]. NHANES includes dietary data from repeated 24-h dietary recall. Average daily sodium intake among US children and adolescents aged 8–18 years was found to be 3,387 mg, a level that exceeds the recommended daily intake limit for sodium intake among adults. Moreover, the study found that sodium intake is associated with systolic BP and risk for prehypertension and hypertension among children and adolescents. A striking finding in the study was that the positive association of sodium intake with BP level was stronger among those who are overweight or

obese. These findings strongly suggest a synergy between overweight/obesity and sodium intake on BP level in children and adolescents.

Other dietary nutrients confer health benefits. The Dietary Approaches to Stop Hypertension (DASH) study in adults with high BP demonstrated the BP-lowering benefits of a diet that was high in fresh fruits, vegetables, whole grains, and low-fat dairy products [37]. Similar large-scale trials have not been conducted in childhood. A small study compared a DASH diet tailored to children and adolescents to standard nutrition counseling in 57 adolescents with hypertension or prehypertension. Among those assigned to the DASH diet, there was significantly greater reduction in systolic BP compared to those who received standard diet counseling [38]. Further investigations on the DASH-style diet in childhood are needed to confirm benefit on BP in the young. However, the preliminary results have been sufficiently compelling to support current recommendations to increase intake of fruits, vegetables, fiber, and dairy in diets of all adolescents.

Outcomes of Childhood Onset Hypertension

There is presently no long-term data to connect a level of childhood BP with cardiovascular events in later adulthood. Despite the absence of such longitudinal data to assess risk for adverse outcomes among adolescents with high BP, data on surrogate markers of vascular injury indicate that vascular pathology does occur even in the young. Left ventricular hypertrophy (LVH) occurs commonly in children and adolescents with confirmed primary hypertension [39–42]. LVH is also detectable in adolescents with prehypertension [43]. Structural changes in forearm vessels of obese adolescents with high BP were detected by Rocchini et al. [44], who observed a significant correlation of peripheral vascular resistance at maximum vasodilation with measures of insulin resistance. Carotid artery intimal-medial thickness (cIMT), assessed by ultrasound, has been found to be greater in young adults who had multiple risk factors since childhood [45, 46]. In smaller cross-sectional studies, an increase in cIMT was already detectable in adolescents with high BP [47, 48]. The Pathobiological Determinants of Atherosclerosis in Youth Study [49], based on autopsy cases of accidental deaths, demonstrated that quantifiable vascular injury is detectable in adolescents and young adults and there is a relationship, even in youth, between early atherosclerotic lesions and cardiovascular risk factors, including high BP, altered lipids, and smoking exposure. Investigators in the Bogalusa Heart Study reported comparable findings in a study that also identified an association between risk factors and early atherosclerotic lesions on autopsy material in youth [50]. In a recent study, digital retinal photographs were used to measure retinal arteriolar caliber in healthy children. The investigators observed that children in the highest quartile of BP had significantly narrower retinal arterioles than those with lower BP, suggesting that higher BP in childhood is associated with alteration in the microvasculature. There is also evidence that some children and adolescents with hypertension have subtle changes in cognitive function, in the domain of executive decision making [51, 52]. Together, the findings described in these reports indicate that a high BP level in childhood is not only a risk factor for future hypertension. Rather the findings are indicative of a process in which signs of vascular injury are detectable in asymptomatic children and adolescents with high BP.

Summary

Based on criteria for definition, primary hypertension and prehypertension are identifiable in children and adolescents [2]. Primary hypertension in childhood is not uncommon, and the prevalence is increasing [3, 8]. The definition of hypertension in childhood continues to be based on the upper segment of the normal BP distribution, and not on outcome data. It is possible that the percentiles currently used to define hypertension and prehypertension in childhood underestimate the longitudinal risk, and future evidence may warrant a lower level to define high-risk BP.

Considering the rates of verified hypertension (>3 %) and prehypertension (>3 %) in asymptomatic children and adolescents, high BP is a common chronic health problem in childhood. Data from clinical studies on high BP in childhood show that primary hypertension in childhood is frequently associated with excess adiposity, including overweight, and other cardiovascular risk factors. It is also apparent that intermediate markers of target organ damage such as LVH, increased cIMT, retinal vascular changes, and subtle cognitive changes are detectable in children and adolescents with high BP. The consequences of these recent findings on are not yet established, and longitudinal BP data extending from childhood into middle adulthood are limited. A few recent reports based on available longitudinal data provide some evidence that high BP in the young can be linked to premature cardiovascular events in adulthood. The onset of primary hypertension in childhood has been shown to be associated with increased rates of premature death (<age 55) in Native Americans [53]. The Coronary Artery Risk Development in Young Adults (CARDIA) study reported that high BP with high body mass index in young African American adults is associated with premature heart failure [54]. It has also been reported that high BP in childhood is associated with a greater risk for development of coronary artery disease in adulthood [55]. These limited reports suggest that pathologic vascular changes, which set the stage for hypertension-related events, may be well under way among some children and adolescents with high BP.

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Epidemiology of Cardiovascular Disease in Children

13

Samuel S. Gidding

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 recently published.

Keywords

Hypertension • Cholesterol • Tobacco • Obesity • Risk factors • Children • Heart disease • Atherosclerosis

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, low HDL cholesterol, elevated triglycerides), tobacco use, and diabetes mellitus [1]. Age, gender (female gender is protective), and genetic endowment are non-modifiable risk factors. Physical inactivity, obesity, family history, adverse nutrition, and low socioeconomic status function as independent risk factors and are intimately related to the development of cardiovascular risk in adults (Table 13.1) [1].

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

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Table 13.1 Risk factors for atherosclerosis

Major modifiable risk factors
Hypertension
Dyslipidemia (elevated LDL cholesterol, low HDL cholesterol, elevated triglycerides)
Tobacco use
Diabetes mellitus
Non-modifiable risk factors
Age
Gender
Genetic history
Factors that modify major risk factors and may be independent themselves
Diet
Physical activity
Family history
Obesity
Low socioeconomic status

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 [2]. 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 post mortem: 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 grades IV and V) are present, that the major 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 [2]. Atherosclerosis in women developed at a pace lagging about 5–10 years behind that in men (Fig. 13.1). 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) [3].

In PDAY, hypertension was evaluated categorically as the measure of hypertension was a renal arterial thickness 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 [4].

Both non-HDL cholesterol and HDL cholesterol were related to atherosclerosis, both in the coronary arteries and the abdominal aorta. The relationship with non-HDL cholesterol is continuous and graded with each 30 mg/dl higher non-HDL cholesterol level increment associated with the equivalent of 2–3 years of vascular aging. The relationship of HDL cholesterol to atherosclerosis was less strong but significant [5].

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 [6].

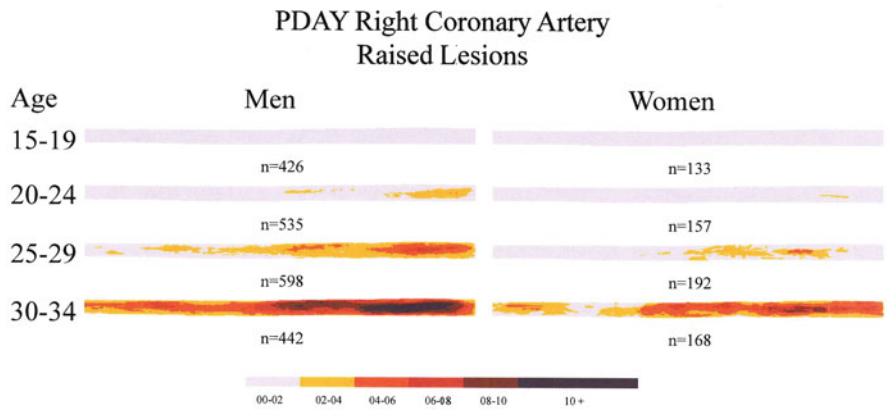

Fig. 13.1 Prevalence map of raised lesions of right coronary arteries by age and sex

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 kg/m^2) was related to atherosclerosis independent of other risk factors in men only [4, 7].

To assess the importance of multiple risk factors on atherosclerosis development, the PDAY risk score was created. Each point in the risk score was gated to 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 chronologic 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 [5]. 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 [8].

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 [9]. Conversely defects associated with low cholesterol are protective against future disease [10]. 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 [11]. For diabetes mellitus, evidence is provided by the natural history of type I 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 [12]. Type 2 diabetes mellitus is increasing in prevalence in adolescents and is associated with obesity, elevated triglycerides, low HDL cholesterol, and hypertension [13].

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 better predicted carotid IMT or calcium on CT scan than risk factors measured at the time of the subclinical atherosclerosis measurement [14-17]. 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 [17, 18]. Thus, improvement in risk as a young adult prevented acquisition of subclinical atherosclerosis (Fig. 13.2).

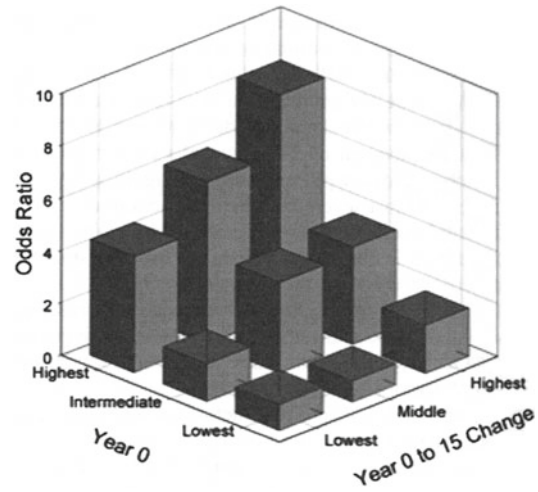

Fig. 13.2 The likelihood of having coronary calcium on CT scan at age 33–45 years is shown by the height of the bars. The groups are defined by tertiles of risk at baseline and change in risk over 15 years. As risk at baseline increases (higher PDAY risk score), likelihood increases. Risk change also impacts change in likelihood of future coronary calcium

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.

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 [19]. Cholesterol levels have a similar tracking coefficient [20]. 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 [3, 17]. 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 % [21]. Maintenance of a low cardiovascular risk state is highly protective against atherosclerosis-related morbidity as is improvement in obesity from childhood to early adulthood [22].

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, absence of diabetes mellitus, and absence of tobacco use [23, 24]. Animal models of atherosclerosis provide complimentary data where the introduction of risk above threshold levels produces disease [25]. 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 [26–28].

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 [29]. For example in heterozygous familial hypercholesterolemia, 28 % of children have coronary calcium present on CT scans [30]. Children with end-stage renal disease, type I diabetes mellitus, and chronic severe hypertension are known to have significantly premature cardiovascular morbidity and/or measurable cardiovascular end organ injury in youth [31, 32]. 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.

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 [1, 9]. Table 13.2 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. Non-HDL cholesterol, the difference between total 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 [1, 2].

For US children, NHANES III provides a distribution of lipid levels. Fasting values are available for adolescents in that study [28]. There is

Table 13.2 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	<75	75–100	≥100
≤9 years			
>10 years	<90	90–130	≥130
	Acceptable	Borderline	Low
HDL cholesterol	≥45	40–44	<40

significant variation in lipid levels by age with values increasing until about 2 years of age, 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 [33]. 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 [34].

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 1:500 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 [9, 35]. Homozygotes have total cholesterol levels in excess of 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 >1,000 mg/dl and require diets with <10 % fat to prevent pancreatitis [36]. 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 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 [23]. 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 [1, 37].

The initial treatment of dyslipidemia is dietary. Table 13.3 provides useful principles of diet management [38, 39]. For elevated LDL and non-HDL cholesterol, a 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 13.3. 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 [40], the National Cholesterol Education Program of the National Institutes of Health, KidsHealth.org, and the American Academy of Pediatrics. For elevated triglycerides (below 750–1,000 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.

Table 13.3 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 *trans* 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 nonfat dairy products on a regular basis
Consume fish, especially oily fish, at least twice a week
Reduce salt intake

Pharmacologic treatment for elevated cholesterol is considered in children over 10 years of age with severely elevated LDL cholesterol and failed dietary management [1]. The algorithm in Fig. 13.3 presents the lipid pharmacologic treatment algorithm from the 2011 guideline on CVD risk reduction in youth [1]. 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 >3 times 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 breast-feeding. 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 [41]. 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 [42, 43].

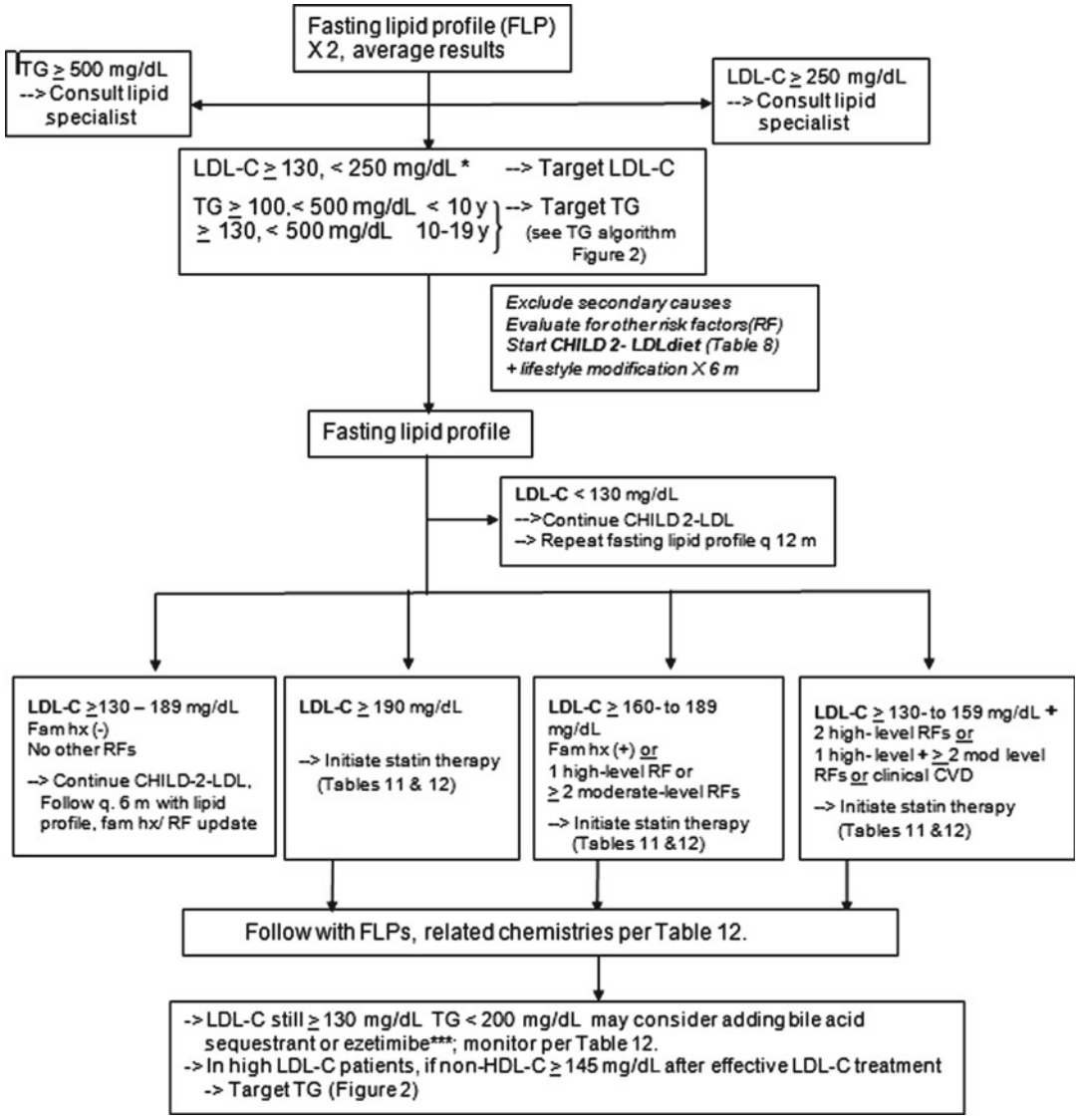

Fig. 13.3 The algorithm for the management of elevated LDL cholesterol, based on the average of two fasting lipid profiles, from the expert panel on integrated guidelines for cardiovascular risk reduction in children and adolescents is shown

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 an LDL level of 160 mg/dl (or 130 mg/dl if risk is considered significantly elevated) is the treatment threshold [32]. Thus, in a patient with hypertension and an additional risk factor, statins would be initiated at this lower threshold. Conversely, blood pressure treatment goals are lower in patients with elevated LDL cholesterol [1].

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.

Tobacco Use

Tobacco use remains the most important preventable cardiovascular risk factor in children [11]. 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 [44]. 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 [11, 45]. Cigarettes, because of nicotine, are highly addicting. It is estimated that smoking 100 cigarettes or less may be sufficient to become an addicted smoker. Though randomized trials suggest physicians can be effective in smoking cessation treatment, success rates are low, particularly in youth [1]. 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 health-care 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 [1, 9]. Since most pediatric health-care providers are inexperienced in smoking cessation treatment, referral to a smoking cessation program or telephone quit line should be considered.

Diabetes Mellitus

In adults, diabetes mellitus is considered a vascular disease equivalent [23]. Cardiovascular disease is the leading cause of death in diabetics. Accelerated atherogenesis is present in both type I and type II diabetes. Diabetes is the only risk factor to erase the gender protection of about 5–10 years in atherosclerosis development in women [2]. Studies of children with type I diabetes mellitus have shown increased carotid IMT; cardiovascular risk factors and age at onset of diabetes influence carotid IMT measurement [46].

The prevalence of both type I and type II diabetes mellitus is rising, the latter because of the obesity epidemic. In adolescents new cases of type II diabetes mellitus are now almost as common as type I [47].

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 [32]. Studies in adults suggest significant cardiovascular event reduction rates, similar to those in nondiabetics, can be achieved with hypertension and lipid-lowering treatment [23].

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. 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 [48]. These factors have been collectively termed the metabolic syndrome in adults. The presence of obesity associated multiple risk tracks into adulthood and in one preliminary study is associated with premature adult morbidity including diabetes [49]. Establishing a pediatric definition has been difficult because of the dynamic nature of risk factors during youth [37]. Nonetheless, the prevention of obesity development in at risk infants and children and the prevention of worsening obesity in affected children and adolescents are important parts 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 [22].

Family history remains an independent risk factor for atherosclerosis [50]. 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 presence of subclinical atherosclerosis [51, 52]. 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 [2]. 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 [53]. A diet low in salt is associated with lower blood pressure [54]. 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 [38]. Excess caloric intake causes obesity.

Higher levels of physical fitness are associated with a small but significant effect on blood pressure and protect against the future development of obesity, hypertension, metabolic syndrome, and diabetes mellitus [55, 56]. It is likely that an above average level of activity reduces the rate of rise of blood pressure over time [57].

Socioeconomic status plays an important role in the evolution of cardiovascular disease risk, particularly with regard to behavioral factors [58, 59]. 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 [60]. The prevalence of specific risk factors also varies by ethnic group [61]. 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 for determining whether or not these nontraditional risk factors substantially improve risk prediction beyond that provided by the major risk factors described previously in this chapter has been established [62]. 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 [63]. These measures are correlated with hypertension and obesity and independent relationships to cardiovascular morbidity are well established. Subclinical atherosclerosis assessments including CT scanning to assess for coronary calcium and cIMT are not useful clinically in children [64]. Calcium does not enter atherosclerotic lesions until young adulthood and normal values for cIMT are age and operator dependent and have not been established [63]. 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 [65, 66]. Pulse wave velocity correlates with presence of elevated blood pressure, diabetes, physical inactivity, and obesity [67].

In adults, the best studied marker of inflammation is C-reactive protein; others include various vascular adhesion molecules and inflammatory cytokines [68]. There is very little pediatric data on these factors and for many, pediatric levels may be different than in adults [69]. There is limited information on tracking, measurement variability, and relationship to adult intermediate endpoints. Since obesity and atherosclerosis are pro-inflammatory, it is unclear if these measures can be considered risk factors or are simply markers of ongoing physiologic processes associated with obesity and the other major risk factors [70]. Nevertheless, the data on markers of inflammation, thrombosis, and adipokines suggest inflammatory and metabolic mechanisms associated with atherosclerosis development in adults are present in youth. Limited trial data suggests adverse levels can be ameliorated by diet and/or exercise. Currently, evidence is insufficient to add these markers to clinical assessment outside of a research setting [68].

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), lipoprotein (a) (a lipid particle that may have prothrombotic activity at least in some isoforms), 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 [71].

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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Part III

Hypertension in Children: Predictors, Risk Factors, and Special Populations

Familial Aggregation of Blood Pressure

14

Xiaoling Wang and Harold Snieder

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. 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 this chapter, therefore, is to review the available literature of twin and family 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

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 [1, 2]. Relatively few observations were made in children in these early studies, which initiated a number of research projects in the 1970s investigating

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whether familial aggregation of BP could be detected in childhood. Zinner et al. [3], 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 [4]. Findings were extended to even younger ages by two further studies that showed significant sibling BP aggregation with 1-month-old infants [5] and significant parent-offspring correlations between mothers and their newborn infants [6].

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. Special 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 [7, 8]. Genetic (or environmental) influences on BP may thus be age dependent in two different manners [9]. First, the magnitude of these influences on BP can differ with age. Second, 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, that is, 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.

Causes of Familial Aggregation of BP

Rationale Behind the Classic Twin Study

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 genetic material. Therefore, special study designs are necessary to discriminate genetic from shared environmental influences. One possibility is the adoption design [10], 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 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 [11].

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., [12]), 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 [11, 13, 14]. Furthermore, BP levels in twins are representative of those in the general population [15, 16].

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 [17, 18]. 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 14.1 and 14.2 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 sizable contribution of genetic factors to BP is overwhelming, with most heritability estimates around 50–60 %.

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. [43] in which heritabilities of BP were estimated in more than 4,000 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 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 [44–46]. Another reason might be that many twin studies may lack the power to detect moderate size influences of common environment [47, 48]. A few studies that either had large sample sizes [39, 41] or used a more powerful multivariate approach [49] 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 in the influences of genetic and environmental factors on the phenotype can take several forms. Although

Table 14.1 Pediatric twin studies estimating heritability (h^2) in systolic (SBP) and diastolic blood pressure (DBP), in ascending order according to age

		Age				h^2	
Study	Pairs of twins	Mean (SD)	Range	Race	Sex	SBP	DBP
Yu et al. [19][a]	274 MZ, 65 DZ	? (?)	0.0–1.0	Chinese	m & f	0.29–0.55	0.27–0.45
Levine et al. [20][b]	67 MZ, 99 DZ	? (?)	0.5–1.0	b & w	m & f	0.66	0.48
Havlik et al. [21]	72 MZ, 40 DZ			Black	m & f	0.46	0.51
	43 MZ, 42 DZ			White	m & f	0.11	0.71
	115 MZ, 82 DZ	7.0 (?)	?	All	m & f	0.23	0.53
Wang et al. [22]	75 MZ, 35 DZ	? (?)	7.0–12.0	Chinese	m & f	0.32	0.46
Schieken et al. [23]	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. [24]	40 MZM, 47 MZF	14.0(6.5)	5.0–50.0	b & w	Male	0.41	0.56
	32 DZM, 36 DZF, 45 DOS				Female	0.78	0.61
Snieder et al. [25]	75 MZM, 91 MZF	14.9(3.0)	10.0–26.0	White	Male	0.57	0.45
	33 DZM, 31 DZF, 78 DOS				Female	0.57	0.45
	52 MZM, 58 MZF	14.6(3.2)	10.0–26.0	Black	Male	0.57	0.58
	24 DZM, 39 DZF, 50 DOS				Female	0.57	0.58
Snieder et al. [7]	35 MZM, 33 MZF	16.8(2.0)	13.0–22.0	White	Male	0.49	0.69
	31 DZM, 29 DZF, 28 DOS				Female	0.66	0.50

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

[a]Range of heritability estimates between 2 months and 1 year are given

[b]Heritability estimates reported by Levine et al. [20] were doubled as outlined by Kramer [26]

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 [50]. 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 14.1 and 14.2. However, heritability estimates for males 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 14.1 and 14.2, most twin studies were conducted in Caucasian populations and a few combined twins from different ethnic groups without reporting separate heritability estimates [20, 24]. 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 [25]. Thus, concurrent with the few other twin studies of non-Caucasians as reported in Tables 14.1 and 14.2, there seems to be no evidence for large differences in BP heritabilities between different ethnic groups. The

Table 14.2 Adult twin studies estimating heritability (h^2) in systolic (SBP) and diastolic blood pressure (DBP), in ascending order according to age

		Age				h^2	
Study	Pairs of twins	Mean (SD)	Range	Race	Sex	SBP	DBP
Sims et al. [27]	40 MZM, 45 DZM	19.4 (3.0)	?	White	Male	0.68	0.76
Ditto [28]	20 MZM, 20 MZF	20.0 (5.0)	12.0–44.0	White	Male	0.63	0.58
	20 DZM, 20 DZF, 20 DOS				Female	0.63	0.58
McCaffery et al. [29]	129 MZ, 66 DZ	21.3 (2.8)	18.0–30.0	94 % white	m & f	0.48	0.51
Bielen et al. [30]	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. [31]	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. [32]	100 MZ, 66 DZ	29.8 (12.0)	?	White	m & f	0.74	0.72
Slattery et al. [33]	77 MZM, 88 DZM	? (?)	22.0–66.0	White	Male	0.60	0.66
Vinck et al. [34]	150 MZ, 122 DZ	34.9 (?)	18.0–76.0	White	m & f	0.62	0.57
Jedrusik et al. [35]	39 MZ, 37 DZ	35.0(8.0)	18.0–45.0	White	m & f	0.53	0.62
Williams et al. [36]	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. [37]	233 MZF, 170 DZF	42.0 (?)	?	90 % white	Female	0.35	0.26
Baird et al. [38][a]	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. [7]	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. [39]	213 MZF, 556 DZF	45.4 (12.4)	18.0–73.0	White	Female	0.17	0.22
Feinleib et al. [40]	250 MZM, 264 DZM	? (?)	42.0–56.0	White	Male	0.60	0.61
Hong et al. [41]	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. [42]	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

For abbreviations see Table 14.1

[a]DBP heritabilities were not reported in the original paper

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 of 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 [51].

To circumvent the disadvantages of conventional BP measures, some twin studies have incorporated 24-h ABP monitoring. Initial studies suggested that 24-h daytime and nighttime SBP and DBP were all heritable, but sample sizes were fairly small [31, 35, 52, 53].

More recently, three twin studies with relatively large sample sizes using ABP monitoring have been conducted. Vinck et al. [34] 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, that is, whether these had one (monochorionic) or two (dichorionic)

outer fetal membranes [54]. Kupper et al. [55] 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 ± SD age: 17.2 ± 3.4; range: 11.9–30.0) from the Georgia Cardiovascular Twin Study [56]. Inspired by evidence from prospective studies showing that nighttime BP is superior to daytime BP as a predictor of cardiac mortality[57], 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. These findings suggest that partly different genes or sets of genes contribute to blood pressure regulation during the daytime compared to the nighttime.

Nocturnal BP fall 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. [58] 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 [56].

Heritability of BP Measured Under Challenged Conditions

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 [59, 60]. 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 [61, 62] 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 recently 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 [63]. 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. [64] 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. [64] 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 recently 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 [65]. 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 [65]. 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 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-h 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.

Recently, based on our 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 for the first time 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 [66].

Influence of Obesity on Familial Aggregation of BP

In subjects of all ages, 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. [67] addressed this question in a pediatric population of 11-year-old twins. They observed highly 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 [68] and females [69] 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 [69].

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 [70]. 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. [71] 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 recent study [72] 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-g 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 1,311 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 [73]. This was confirmed by a recent meta-analysis [74] in 3,901 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 [38].

Age Dependency of Genetic 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 [7]. 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 14.1 (mean age < 18 years) and Table 14.2 (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 [19, 20] 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 above-mentioned study of Vinck et al. [34] specifically investigated the stability of heritable and environmental influences on both conventional and ambulatory BP in three age groups: 18–29, 30–39, and ≥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, Morton, and Rao [75]. 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. [76], who measured SBP and DBP for 1,141 parent pairs aged 48–51. Twenty to 30 years later, blood pressures for 2,497 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 [41, 77]. 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. [76] 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 [75, 77, 78], while estimates from twin studies are typically in the 0.40–0.70 range for both SBP and DBP [43] (see also Tables 14.1 and 14.2).

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 14.1 and 14.2. Second, different genes could influence BP in childhood and adulthood. This possibility is still compatible with the data presented in Tables 14.1 and 14.2, 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. [79]. 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. [79] 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 [80], 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 [7]. 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. [79] (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. [81] analyzed resting SBP and DBP in 254 MZ and 260 dizygotic (DZ) male middle-aged twin pairs (average age 48 years) and again nine 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 [82]. That is, no evidence was found for new genes being switched on or off at different points in time. This was confirmed in two recent studies of Dutch and Australian twins [83, 84] 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 recently conducted the first longitudinal twin study on BP [85] 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 follow-up of our twin sample will enable us to determine at what age the genetic component stabilizes (i.e., at what age no further novel genetic effects are expressed).

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 [86–88], making BP at a young age an important predictor of adult levels [89]. 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 [90, 91].

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The Role of Dietary Electrolytes and Childhood Blood Pressure Regulation

15

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Abstract

The prevalence rates of high blood pressure and cardiovascular risk have increased in youth, given the increasing rates of overweight and obesity. Dietary electrolytes play an important role on influencing blood pressure (BP) mechanisms in youth, and previous research indicates that dietary sodium, potassium, and calcium significantly affect 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 intervention studies demonstrate that reduced intake of sodium is beneficial for BP, it is not clear whether children and adolescents can comply with long-term efforts to reduce sodium intake. There is a growing body of evidence that increased potassium and calcium intake also reduces risk of high BP in youth, and studies suggest that some youth may be more likely to comply with these diets, which emphasize adding foods (e.g., foods containing potassium and calcium), rather than eliminating foods as in 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

Dietary electrolytes • Blood pressure • Children • Sodium • Potassium

Introduction

Although the prevalence of hypertension (HTN) is relatively low during childhood and adolescence [1], an estimated 2.6–3.4 % of children and adolescents have hypertensive blood pressure (BP) levels and 5.7–13.6 % have prehypertensive BP levels [2, 3]. BP patterns have been shown to

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track from childhood to the third and fourth decades of life [1, 4], and elevated BP has been associated with increased risk of cardiovascular and renal diseases [5]. Hypertension and cardiovascular risk have also increased given the growing rates of overweight and obesity, with recent studies showing that obese girls have six times the prevalence rate of HTN as compared to nonobese girls [6]. Thus, there is a strong need for prevention programs to reduce these risks in youth [5, 7, 8]. Modifying intake of dietary electrolytes such as sodium and/or potassium has been an effective approach to BP reduction in adults [9–11], but there is less evidence for the benefit of this approach in children and adolescents [12].

Current recommendations for primary prevention of HTN from the American Heart Association and the National Heart, Lung, and Blood Institute [13–16] involve a population approach and an intensive strategy for targeting individuals who are 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, the sodium consumption of children and adolescents exceeds intake recommendations, with cereals, meat products, and fast food contributing to the problem [17]. Evidence also suggests that addressing obesity-related through weight reduction programs may be more effective when physical activity is incorporated into the intervention, and regular aerobic activity is strongly recommended for improving BP [18–21].

Identifying precursors or markers of HTN in youth is important for preventing the development of primary HTN. Two such markers include cardiovascular reactivity (CVR) and ambulatory BP profiles [18–20]. Cardiovascular reactivity is a measure of vasoconstriction in response to psychological or physical stressors. As a marker, hyperreactivity is conceptualized as a consequence of preexisting cardiovascular damage or of heightened sympathetic tone that results in vasoconstriction and/or excessive cardiac output. As a mechanism, hyperreactive peaks are proposed to damage the intimal layer of arteries, contributing to arteriosclerosis and subsequent HTN. Although there is controversy about the predictive value of CVR, prospective studies have shown that increased CVR to mental stress is predictive of later development of primary HTN [19, 22–26], although efforts to associate it with physiological correlates of HTN (i.e., left ventricular hypertrophy) have yielded mixed results [18, 27–30].

Ambulatory BP profiles may be an important predictor or risk factor of future HTN in youth. Ambulatory BP monitoring (APBM) is a method for assessing individuals' daily fluctuations in BP and for identifying and evaluating factors associated with individual differences in BP responses in the natural environment. Previous research indicates that most people display lower BP values at nighttime during sleeping hours and higher BP values during waking hours [20]. In healthy individuals, 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, however, is shifted upwards throughout the 24-h period [31]. A number of studies suggest that a blunted nocturnal decline in BP may be associated with greater cardiovascular risk [20]. For example, ambulatory BP non-dipping status (defined as < 10 % decrease in BP from waking to sleeping) is a risk factor for the development of end-organ disease in primary HTN. Specifically, patients who are characterized as non-dippers show a more frequent history of stroke and left ventricular hypertrophy (LVH) [32–34]. Studies from our laboratory indicate that even among healthy African-American adolescents, there is a 30 % prevalence rate of non-dipping status [35, 36], and other investigators have shown that racial differences in sodium excretion may be due in part to renal retention of potassium [37]. These findings have led us to investigate the dietary electrolyte factors 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 [38–41]. At the cellular level, electrolytes are positively and negatively charged ions that moderate the

conduction of electrical signals between cells and influence homeostasis within the body [42]. Electrolyte balance (i.e., balance of positively and negatively charged conductive ions) is essential for health [38]. Previous studies indicate that environmental and genetic factors can influence BP responses in children [43–46]. Children as young as 0–3 years of age may be at higher risk for future cardiovascular complications because of differences in sodium handling [47], and stress-induced excretion is a heritable phenotype which differentially affects African-Americans as compared to Caucasians [43, 48]. Other investigators have demonstrated that positive changes in dietary electrolytes in the first two decades of life can reduce BP and cardiovascular risk [39, 40, 49, 50]. Although the beneficial effects of decreasing sodium intake on BP have been more strongly supported than the effects of increasing potassium, fewer studies have been conducted that evaluate the influence of potassium on BP levels in youth [51].

The purpose of this chapter is to summarize the nutritional electrolyte-related determinants of BP in children and adolescents. In particular, this 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 should also be noted. Several investigators have demonstrated positive effects of calcium supplementation on blood pressure generally [52] and in youth [53–55, 56]. In a 2-year family-based intervention, calcium and potassium supplementation were as effective as sodium restriction at reducing BP in hypertensive youth [57]. In addition, an 8-week and a 12-week intervention showed positive effects of calcium supplementation were greater for youth with lower baseline calcium intake [53, 56].

Dietary Sodium and Blood Pressure in Youth

Previous research suggests that casual BP is important in understanding the influence of genetic, environmental, and nutritional influences 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 [39]. The magnitude of the association was noted to be similar to that observed in a meta-analysis by Simons-Morton and Obarzanek that evaluated the effects sodium reduction on BP responses in youth [51]. They critically evaluated 25 observational studies examining the association between sodium intake and casual BP in children and adolescents. Eight of the used self-report measures of dietary intake and 17 used urinary sodium excretion. Approximately 67 % (two-thirds) of the studies including urine collections that controlled for other factors (e.g., age, BMI, weight) in the analysis found a significant positive association with casual BP. One-third of the studies that had no control variables found a significant association with casual BP. Three of the four studies which relied on self-report 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 provide fairly consistent support for the role of sodium intake on BP regulation in children and adolescents. Intervention studies that aim to reduce the intake of sodium may be beneficial, although it is not clear whether children and adolescents can comply with long-term recommendations to reduce sodium intake.

Prior research shows that individuals who are at risk for cardiovascular complications such as African-Americans, hypertensive patients, and those with a positive family history of HTN are more likely to be saltsensitive [58, 59] (i.e., show increased BP in response to high sodium intake). Some of our work examined the prevalence of salt sensitivity in normotensive African-American adolescents [60], 22 % of healthy normotensive African-American adolescents characterized as saltsensitive based on definitions established in the adult literature [61]. 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 [59]. In another study by Palacios et al., African-American girls showed greater sodium retention in response to a low-sodium diet (57 mmol/d) than Caucasian girls, suggesting that sodium handling may contribute to underlying racial differences in susceptibility to developing HTN [62].

Several investigators have also examined the relationship between salt sensitivity and ambulatory BP profiles in children and adolescents. Wilson et al. examined the relation between salt sensitivity and ambulatory BP dipping status [63]. 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 individuals. Harshfield et al. also demonstrated that sodium intake is an important determinant of ambulatory BP profiles in African-American children and adolescents [64]. These findings are consistent with those of de la Sierra et al. who demonstrated higher awake BP values in normotensive salt-sensitive than in salt-resistant adults [65].

Rocchini et al. conducted a series of studies examining BP sensitivity to sodium intake in obese adolescents [66]. Obese adolescents showed greater decreases in casual BP after a shift from high to low sodium intake compared to nonobese adolescents. This BP sensitivity to the alteration of sodium intake was also positively correlated with plasma insulin concentration and with hyperinsulinemia [66]. Consequently, sodium retention may be a mechanism underlying the higher concentrations of plasma insulin in obese adolescents. In another study by Lurbe et al. 85 obese and 88 nonobese children (ages 3–19 years) participated in 24-h ABPM and had their urinary sodium excretion rates determined [67]. The interaction between sodium excretion and weight was negative, indicating a smaller rate of change in BP by sodium unit for obese than for nonobese participants. However, obese participants experienced higher ambulatory BP levels associated with the same levels of sodium excretion than nonobese 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.

Salt sensitivity has also been associated with non-dipping status in adults [33, 34]. The relationship between sodium intake and nocturnal BP has been studied by several investigators. Uzu et al. found that non-dipper nocturnal BP in salt-sensitive patients was normalized to a dipper pattern (drop from awake to asleep) with sodium restriction [68]. Higashi et al. also demonstrated that nocturnal decline in mean BP was significantly smaller in salt-sensitive patients with hypertension when compared to salt-resistant subjects with hypertension during a sodium-loading protocol [69].

The mechanism by which sodium sensitivity alters nighttime BP likely involves the sympathetic nervous system (SNS). SNS arousal has been associated with differential handling of sodium following a behavioral challenge (video games) among individuals who are identified as retainers (those who show little excretion of sodium load in urine) [70]. In a biracial sample of normotensive children, Harshfield et al. demonstrated a stronger relationship between sodium handling and casual BP in African-American adolescents [64]. Harshfield et al. also showed that African-American adolescents had a stronger association between 24-h urinary sodium excretion, casual BP, and BP during sleep, independent of the urinary potassium excretion, than Caucasian adolescents. For casual BP and nighttime ambulatory BP, the slope was positive and significant for African-Americans, but no relationship was shown for Caucasian adolescents. The findings reported by Harshfield and colleagues [64, 70], and other investigators [71], suggest an interactive role for the SNS in sodium retention which may, in part, explain blunted nocturnal decline in ambulatory BP profiles observed in salt-sensitive individuals. Additionally, sleep deprivation has been shown to lead to natriuresis and excess diuresis, as well as higher nighttime blood pressure and heart rate in healthy children [72]. This indicates another potential pathway through which SNS arousal may impact BP.

Dietary Potassium and Blood Pressure in Youth

Although the beneficial effects of decreasing sodium intake on BP have been more strongly supported than the effects of increasing potassium, there is also growing evidence of the positive influence of potassium on BP levels in youth. For example, in the review by Simons-Morton and Obarzanek [51], 12 observational studies examined the association of potassium intake and casual BP in children and adolescents. Nine of the observational studies used urinary measures of potassium excretion, and six of these studies controlled for other factors such as weight. Two of these studies showed a significant inverse relationship between potassium intake and casual BP, while three studies showed no relationship. One study showed an unexpected positive association between potassium intake and casual BP. Two studies that relied on self-report estimates of intake showed a significant inverse relationship between potassium intake and systolic or diastolic BP, while two additional studies showed no relationship. Taken together, these studies provide support for a beneficial effect of high potassium on casual BP levels in youth. However, as we have previously noted [36], the effects of potassium may be most pronounced among salt-sensitive individuals, such as among African-Americans, or those with a positive family history of HTN. These factors were not specifically addressed in Simons-Morton and Obarzanek's review of the literature [51].

Research examining the effects of potassium intake on CVR has been scarce. In general, these studies have been correlational and have shown beneficial effects in only a subgroup of individuals. For example, Berenson and colleagues reported that African-American boys in the highest BP strata, who showed significant increases in BP reactivity, had lower urinary potassium excretion than Caucasians [73]. Among adult populations, Morgan et al. demonstrated in hypertensive patients that potassium supplementation (48 mmo1/24 h) prevented the increase in BP produced by postural changes [74].

Few reports have characterized the relationship between plasma potassium and ambulatory BP in adults. Goto et al. showed a significant negative association between daytime plasma potassium concentration and 24-h systolic and diastolic BPs in patients with primary HTN [75]. Plasma potassium was also inversely correlated with daytime and nighttime systolic and diastolic BP levels. Interpreting the relationship between a plasma electrolyte such as potassium and BP is difficult, however, because there are many factors known to influence plasma potassium values [76], [77]. Although there are limitations of plasma potassium values, these results are consistent with prior epidemiological studies, which have shown associations between potassium intake, potassium excretion, and BP levels [78].

Nutrition Interventions and Blood Pressure in Youth

A number of studies to date 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 [79], average sodium intakes of urban children and adolescents in Philadelphia well exceeded their nutritional needs, determined by 24-h dietary recall assessments. These data are consistent with the Bogalusa Heart Study, a study that also assessed electrolyte intake among infants and children living in a rural biracial community [80]. In another study by Pomeranz et al. increased BP levels were found among infants who received formula mixed with high-sodium tap water (196 mg/l) as compared to infants who received formula mixed with low-sodium mineral (32 mg/l) at 6 weeks of age [81]. One randomized controlled trial examining the impact of maternal calcium supplementation during pregnancy on infant blood pressure in West Africa found that calcium was unrelated to offspring blood pressure [82].

Among older youth, Cullen et al. had 5,881 adolescents and young adults (aged 14–21 years) complete a survey on Youth Risk Behavior [83]. Potassium intake related to fruit consumption

declined for males and females during the high school years. Consistent with this finding, Neumark-Sztainer et al. reported that among 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 [84]. Several investigators, including Berenson et al. [64, 85, 86], have also reported that African-American children and adolescents show lower urinary potassium excretion rates than same-age Caucasians. Thus, targeting adolescents and especially minority adolescents for dietary interventions that emphasize high-potassium/low-sodium food choices may be particularly needed during the adolescent stage of development, when emphasis on the importance of nutrition in youth seems to deteriorate.

Dietary electrolytes such as sodium, potassium, and the ratio of sodium/potassium are important in BP regulation. A number of studies have examined the influence of altering electrolyte intake on BP responses in children and adolescents. Table 15.1 provides a summary of the interventions in youth that have studied the effects of either reduced sodium intake, increased potassium intake, or the combination on BP responses. In general, the evidence is inconsistent but suggests that reducing sodium intake and increasing potassium intake seem to be effective strategies. However, further research is needed to determine the long-term compliance of such interventions in youth.

In a meta-analysis by He and MacGregor [39], 10 trials were evaluated and it was shown that sodium reduction (ranging from 42 % to 54 %) in children demonstrated immediate decreases in BP. In a study by Miller et al. [87], the effects of sodium restriction for 12 weeks (60 mEq/24 h) were evaluated on BP responses in Caucasian youth ages 3–30 years. They found 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 significant decreases in casual BP in Caucasian children during sodium restriction ranging from 4 weeks to 1 year of age [88, 89].

Researchers have demonstrated that subgroups of children and adolescents show greater decreases in BP responses to changes in sodium restriction. For example, Rocchini et al. demonstrated that obese adolescents had significantly greater decreases in mean BP than nonobese adolescents when they went from a high-sodium diet to a low-sodium diet [90]. Other researchers have also demonstrated greater reductions to alterations in sodium intake on casual BP responses in African-American children compared to Caucasian children [91].

In their review paper, Simons-Morton and Obarzanek also identify 11 relevant 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 [51]. 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 11 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^2. One study that evaluated the effects of increasing potassium was the Dietary Intervention Study Children (DISC). Participants enrolled in this study had elevated low-density lipoprotein cholesterol. Assessments were done at baseline, 1 years, 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. tested the feasibility of years potassium supplementation or sodium reduction in preventing the rise in BP among adolescents [12]. Adolescents who were in the upper 15th percentile of BP distribution were randomly assigned to

Table 15.1 Effects of dietary sodium and potassium interventions on blood pressure in youth

Authors	Intervention	Sample baseline demographics	Compliance	Findings
Sodium interventions				
Whitten et al. 1980 (United States) [115]	Two group RCT	*N* = 27 (F = 0, M = 27)	*24-h UNa:* Samples were collected for 3 days via metabolic frames. Na concentration was 11.3 mmol/d in the LS group and 54.8 mmol/d in the CTL group	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-years 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
	Duration = 5-months/group with 8-years follow-up *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 *Control group (CTL; n = 14)* Commercially available foods with sodium included (9.25 mmol/100 kcal) were provided to parents and fed to infants	Healthy African American male infants. *Age (months)* = 3 *Race* = 100 % African American *Mean BP* = not reported	*Food records:* Records showed a reduction in sodium intake consistent with UNa findings	
Gillum et al. 1981 (United States) [88]	Two group RCT	*N* = 80 children + their families (F = 61 % FEP; F = 31 % CTL)	*Food records (3 days):* The FEP group reported significantly lower sodium intake than the CTL group (~25 mmol decrease)	Based on 3-days food records 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
	Duration = 1-year	Children with SBP > 95th percentile for age and sex but SBP <130 and DBP <90 mmHg from the Minneapolis, MN public school system	*24-h UNa:* 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	Urinary sodium excretion did not differ between groups

(continued)

Table 15.1 (continued)

Authors	Intervention	Sample baseline demographics	Compliance	Findings
	Family education program (FEP; n = 41 [children + families])	*Mean age (year)* = 7.8 ± .7 (FEP); 8.0 ± .8 (CTL)		Blood pressure did not differ by group or change over time
	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	*Race* = not reported		
	Control group (CTL; n = 39) No treatment	*Mean BP* = 111/65 (FEP); 115/69 (CTL)		
Trevisan et al. 1981 (United States) [116]	Two group RCT	*N* = 21	*24-h UNa:* There was a significant reduction in erythrocyte Na concentration in the LS group but no change in the CTL group. Random samples and duplicate meals were collected but results were not reported	Erythrocyte sodium concentration was reduced and a nonsignificant decline in SBP was observed in the LS group (−1.25 ± 4.96 mmHg)
	Duration = 10 weeks/group	Male and female students from a boarding high school		
	Low sodium diet (LS; n = 12)	*Age (year)* = 11–15		
	Diet included reduction of sodium intake by ~ 70 %	*Race* = not reported		
	Control group (CTL; n = 9)	*Mean SBP* (mmHg) = 108 (LS); 111 (CTL)		
	Diet similar in composition to control but without reduced sodium			
Hofman et al. 1983 (Netherlands) [117]	Two group RCT	*N* = 466 (F = 49 %, M = 51 %)	*Spot UNa:* Na concentration was 22.7 mmol/L in the CTL group and 11.1 mmol/L in the LS	The LS formula group demonstrated decrease in SBP at 25 weeks (−2.00 ± 2.13 mmHg)
	Duration = 6-months	Newborn infants born within 1-month of each other	*Baby food delivered:* Mean Na consumed based on number of food deliveries was estimated to be 2.5 mol of Na in the CTL group and .89 mol of Na in the LS group	
	Low sodium infant formula (LS; n = 225) Commercially available formula with 33 % the concentration of sodium as the control formula	*Age (week)* = 1 *Race* = not reported		
	Control group (CTL; n = 241) Commercially available formula with sodium included (9.25 mmol/100 kcal) were provided to parents and fed to infants	*Mean SBP (mmHg)* = 88 (LS); 87 (CTL)		

Cooper et al. 1984 (United States) [118]	Two group crossover RCT	*N* = 113 (F = 66, M = 47)	*Overnight UNa:* 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 3 random participants per group per week. Food samples were in close agreement with UNa	Sodium intake was reduced by ~ 58 % and SBP and DBP decreased nonsignificantly (−.6 ± .70 mmHg; −1.40 ± 1.0 mmHg) following the LS diet
	Duration = 24-days/condition	Adolescent students from a boarding high school without HTN or chronic illness		Participants with BMI below the median had significant decreases in SBP after the LS diet ($p < .05$). Body size may influence BP response to sodium reduction
	Low sodium diet (LS)	*Mean age (year)* = 16		
	Diet included reduction of sodium intake by ~ 200–60 mmol/d via controlled cafeteria meals. Children were instructed not to add salt or condiments to meals and between meal snacks were provided	*Race* = not reported		
	Control group (CTL)	*Mean SBP(mmHg)* = 109/61		
	Meals were same as LS group but without reduced sodium			
Calabrese and Tuthill 1985 (United States) [119]	Two group RCT	*N* = 153 (F = 75, M = 78)	*First-morning UNa:* 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
	Duration = 12-weeks/group	Fourth grade school children in a community with high sodium in their water distribution system. Children were matched by sex, school, and baseline BP		Lack of effects for boys may have been due to undetected poorer compliance in boys, or other explanations
	Low sodium water (LS; n = 51)	*Mean age (year)* = 9		
	Bottles water with low sodium water (10 mg/L) was provided to children for drinking and family meal preparation, and in school classrooms	*Race* = not reported		
	Control (CTL; n = 102)	*Mean BP (mmHg)* = 99/58		
	Bottled water with higher sodium (110 mg/L) was provided to children for drinking and family meal preparation, and in school classrooms			

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Table 15.1 (continued)

Authors	Intervention	Sample baseline demographics	Compliance	Findings
Howe et al. 1985 (Australia) [120]	Two group crossover RCT	*N* = 21 (F = 48 %, M = 52 %)	*Overnight UNa:* Na/creatinine ratio changed from 179.1 to 101.7 mmol.24 h	Overnight UNa demonstrated a reduction in sodium intake of 43.3 %. A slight decrease in DBP was demonstrated (−1.3 ± 1.8 mmHg)
	Duration = 3-weeks/condition	Prehypertensive or hypertensive adolescents	*Food records:* Records showed a reduction in sodium intake consistent with UNa	
	Low sodium water (LS)	*Mean age (year)* = 11–14		
	Parents and children were interviewed by a dietician who provided detailed instruction on adhering to a low sodium diet	*Race* = not reported		
	Control group (CTL) no treatment	*Mean BP (mmHg) = 119/78*		
Tuthill and Calabrese 1985 (United States) [121]	Three group RCT	*N* = 216 (F = 75, M = 78)	*24-h UNa:* 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
	Duration = 12-weeks/group	Ninth through twelfth grade adolescent girls in a private boarding school. Children were matched by sex, school, and baseline BP		
	Morning sodium capsule (MS)	*Mean age (year)* = 9		
	Participants took one capsule containing 2 g of sodium in the morning and one placebo capsule in the evening each day	*Race* = not reported		
	Evening sodium capsule (ES)	*Mean BP* = 99/57 mmHg		
	Participants took one placebo capsule in the morning and one capsule containing 2 g of sodium in the evening each day			
	Placebo control (CTL)			
	Participants took two placebo capsules each day			

Tochikubo et al. 1986 (Japan) [122]	Two group RC	*N* = 197 (F = 17; M = 180)	*24-h UNa and UK:* 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	The LS group did not reduce blood pressure, but sodium excretion (−52 mEq/d), weight (−1.7 kg), and BP (−12/7 mmHg) decreased significantly in the LS+S group
	Duration = 10-weeks/group	Borderline hypertensive (BHT) and normotensive (NT) students from six high schools in Japan	Na concentration was significantly higher in the BHT group and K concentration was significantly lower	Blood pressure of BHT adolescents may be decreased with dietary education and self-monitoring
	Low sodium counseling and self-monitoring (LS+S; n = 12)	*Age (year)* = 15–18		
	Hypertension education and diet counseling including self-monitoring of urinary Cl excretion	*Race* = not reported		
	Low sodium counseling (LS; n = 9)	*Mean SBP (mmHg)* = 150.3 ± 9.8 (BHT); 117.7 ± 12.2 (NT)		
	Hypertension education focusing on lowering sodium intake			
Miller et al. 1988 (United States) [87]	One group CT	*N* = 149 (F = 85, M = 64)	*Weekly UNa:* Na concentration decreased from baseline to 41.1 ± 1.9 mmol/d (F) and 53.5 ± 3.6 mmol/d (M) at the end of the LS diet	In both sexes there was a significant change in sodium excretion ($p < .001$) 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 ($p < .05$). Results suggest that compliance to modest sodium restriction may not consistently lower BP in normotensive children
	Duration = 12-weeks	Normotensive identical twin pairs, siblings and parents recruited through a research twin panel and local schools		
	Low sodium diet (LS)	*Mean age (year)* = 9.7 ± .4 SEM (F); 10.6 ± .7 SEM (M)		
	Families were instructed to reduce sodium intake to 60 mmol/d to ensure a reduction to 75 mmol/d. Families were instructed to otherwise maintain usual dietary practices	*Race* = 100 % Caucasian		
		Mean BP(mmHg) = 91/54 (F); 95/55 (M)		

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Table 15.1 (continued)

Authors	Intervention	Sample baseline demographics	Compliance	Findings
Ellison et al. 1989 (United States) [123]	Two group crossover CT	*N* = 2 schools (F ~ 51 %, M ~ 49 %)	*Food records:* 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, $p < .01$) and DBP significantly decreased also (−1.5 mmHg, $p < .01$)
	Duration = 6-months/conditions:	Male and female students from two boarding high schools in the northeastern U.S.		
	Low sodium diet (LS; 309 students)	*Mean age (year)* = 15		
	Diet included reduction of sodium intake by ~ 15–20 % via controlled cafeteria meals and changes in food purchasing and preparation	*Race* = ~77 % Caucasian		
	Control group (CTL; 341 students)	*Mean BP (mmHg)* = 107/64		
	Meals were same as LS group but without reduced sodium			
Myers 1989 (Australia) [124]	Two group crossover RCT	*N* = 23 (F = 100 %; M = 0 %)	*24-h UNa:* Na concentration changed from 158 to 66 mmol/24 h	Sodium intake was reduced by 58.2 % based on UNa in the LS group. Both SBP and DBP decreased in the LS group (−3.74 ± 2 mmHg; −1.70 ± 2.17 mmHg)
	Duration = 2-weeks	Female sodium sensitive (SS) and insensitive (SI) children and adolescents whose parents were affiliated with a hospital in Newcastle, NSW		
	Low sodium diet (LS)	*Mean age (year)* = 9 (SS); 12 (SI)		
	Participants were advised by a dietician to reduce sodium intake (77 ± 37 mmol/d). Advice was based on previous diet history and 24-h UNa	*Race* = not reported		
	High sodium diet (HS)	*Mean BP (mmHg)* = 108/67		
	Participants were advised to increase sodium intake (201 ± 37 mmol/d). Advice was based on previous diet history and 24-h UNa			

Nader et al. 1989 (United States) [110]	Two group RCT	*N* = 206 families (623 persons)	*Food records, 24-h recall, food frequency questionnaire:* 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
	Duration = 1-year/group	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		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
	Low sodium/low fat diet (LS)	*Mean age (year)* = not reported		
	Three months of intensive educational group sessions promoting decreased sodium and fat intake and increased physical activity followed by 9 months of maintenance sessions	*Race* = 26 % Caucasian families; 46 % Mexican American families		
	Control group (CTL) no treatment	*Mean BP (mmHg)* = not reported		

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Table 15.1 (continued)

Authors	Intervention	Sample baseline demographics	Compliance	Findings
Rocchini et al. 1989 (United States) [90]	Two group crossover RCT	$N = 78$	*Food records:* Records analyzed for six randomly selected days during the low sodium diet indicated that obese and nonobese participants had similar sodium intake (15.9 ± 4.5 vs. 14.8 ± 2.6 mmol/d)	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 ± mmHg vs. +1 ± 2 mmHg; $p < .001$)
	Duration = 2-weeks/condition	Obese ($n = 60$) and nonobese ($n = 18$) unmedicated adolescents recruited through pediatricians and school nurses		BP in obese adolescents may be more sensitive to sodium intake
	Low sodium diet (LS)	*Mean age (year)* = 12.5 ± .5 SEM (obese); 12.5 ± .6 SEM (nonobese)		
	Participants adhered to a 4-days rotating meal plan with meals containing 20–30 mmol/d of sodium	*Race* = not reported		
	High sodium diet (HS)	*Mean BP(mmHg)* = 125/74 (obese); 106/64 (nonobese)		
	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			
Howe et al. 1991 (Australia) [125]	Two group crossover RCT	$N = 100$ (F = 48 %, M = 52 %)	*First-morning UNa:* Na concentration decreased from 175.9 to 101.8 mmol/d in the LS condition	Sodium intake decreased by ~ 42 % in the LS condition and both SBP and DBP declined (−97 ± .68 mmHg; −.56 ± .71 mmHg)
	Duration = 4w/condition	School children representing the top, middle, and bottom deciles of the blood pressure range	*Food records:* A subset of participants completed records and showed a reduction in Na intake consistent with UNa findings	
	Low sodium diet (LS)	*Age (year)* = 11–14		
	Weekly dietary counseling for both children and parents with low-sodium bread provided	*Mean SBP* = 115/60 mmHg		
	Control group (CTL)			
	Weekly dietary counseling for both children and parents with salt sachets provided			

Gortmaker et al. 1999 (United States) [112]	Two group CT	*N = 14 schools, 479 students* (F = 56 % EWKM; F = 61 % CTL)	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 ($p = .01$)
	Duration = 2-years	Children in grades four and five from public schools in Baltimore, MD		
	Eat well and keep moving program (EWKM; n = 6 schools)	*Mean age (years)* = 9.2 (EWKM); 9.1 (CTL)		
	Classroom teachers gave materials focused on decreasing high fat foods and television watching, and increasing fruit and vegetable intake and physical activity. The program provided links to school food services and families and wellness training programs to teachers	*Race* = 91 % African American		
	Control group (CTL; n = 8 schools)	*Mean BP (mmHg)* = 115/60		
	No treatment			
Wilson and Ampey-Thornhill 2001 (United States) [109]	One group clinical trial	*N* = 184 (F = 101, M = 83)	*24-h UNa:* Compliance was defined as <50 mEq/24 h during the LS diet. Based on these criteria 77 % of adolescents were compliant ($n = 114$)	SBP trended toward decreasing in compliant participants but decreases were nonsignificant
	Duration = 5-days	Healthy normotensive, unmedicated African American adolescents recruited from schools, churches, and local recreation centers in the southeastern U.S.		Compliant girls reported higher levels of familial dietary support, whereas compliant boys reported lower levels of familial dietary support
	Low sodium diet (LS)	*Mean age (year)* = 14 ± 1(F); 14 ± 1 (M)		Higher dietary support may be associated with adherence in girls
	Children and families were given guidelines and several food items for maintaining a low sodium diet	*Race* = 100 % African American		
		Mean BP (mmHg) = 101/56 (compliant F); 5108/53 (compliant M)		

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Table 15.1 (continued)

Authors	Intervention	Sample baseline demographics	Compliance	Findings
Pomeranz et al. 2002 (Israel) [81]	Three group RCT	*N* = 58	*Spot UNa/creatinine:* 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	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
	Duration = 8-weeks/group	Newborn Jewish infants in a university-affiliated hospital. Infants from families with history of HTN excluded		At 24-weeks follow-up BP values in the LS group increased toward those of the HS group
	Low sodium formula (LS; n = 25)	*Mean Age (week)* = 40 ± 1.3 (LS); 40.2 ± 1.1 (HS); 39.5 ± 1.6 (CTL)		
	Infant formula diluted with water with 1.4 mmol/L sodium concentration	*Race* = not reported		
	High sodium formula (HS; n = 33)	*Mean BP (mmHg) = not reported*		
	Infant formula diluted with water with 8.5 mmol/L sodium concentration			
	Control group (CTL; n = 15)			
	Infants were breastfed			

Palacios et al. 2004 (United States) [62]	Two group crossover RCT	*N* = 36 (F = 100 %; M = 0 %)	*24-h UNa:* 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	Blood pressure significantly decreased ($p < .05$) from baseline to the end of the study
	Duration = 2-months/condition	Matched African American (*n* = 22) and Caucasian (*n* = 14) normotensive adolescent females		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
	Low sodium diet (LS)	*Mean age (year)* = 12.4 (African American); 13.2 (Caucasian)		
	1 g/day, 43 mmol/d of sodium with fixed amounts of dietary potassium	*Race* = 39 % Caucasian, 61 % African American		
	High sodium diet (HS)	*Mean BP (mmHg)* = 113/59 (African American); 113/55 (Caucasian)		
	4 g/day, 174 mmol/d 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			
Couch et al. 2008 (United States) [49]	Two group RCT	*N* = *57* (F = 21, M = 36)	Compliance not reported	The DASH group showed a greater decrease in SBP than the RC (−7.9 % vs. −1.5 %, $p < .01$)
	Intervention = 3-months/group	Prehypertensive or hypertensive adolescents seeking treatment in a children's hypertension clinic		There was an increase for DASH participants in fruit servings among DASH participants, with fruit servings increasing by ~ 2/day and intake of high sodium/fat foods decreasing by ~ .8 servings/day
	DASH Diet (DASH; n = 29)	*Mean age (year)* = 14.3 ± 2.1 (DASH); 14.4 ± 2.1 (RC)		Intake of potassium and magnesium reportedly increased by 42 % and 36 % respectively
	Initial counseling session with dietician to follow a modified DASH diet. Eight weekly and 2 biweekly phone calls with interventionists and biweekly mailings	*Race* = 40 Caucasian, 17 African American		
	Routine care(RC; n = 28)	*Mean BP (mmHg)* = 131/79 (DASH); 126/82 (RC)		
	Initial counseling session with dietician encouraging consumption of fruits, vegetables, grains, lean meats and low fat dairy			

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Table 15.1 (continued)

Authors	Intervention	Sample baseline demographics	Compliance	Findings
Potassium interventions				
Wilson et al. 1996 (United States) [35]	Two group RCT	*N* = 40 (F = 18, M = 22)	*24-h Urinary potassium:* 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 post-treatment (119/67–114/64), but increased for nondippers (115/62–124/67)
	Duration = 4-weeks/group	Healthy normotensive African American adolescents classified as dippers (>10 % BP decrease from waking to sleeping; *n* = *28*) and nondippers (≤10 % BP decrease from waking to sleeping; *n* = 12)		Seventy-five and 80 % of nondippers switched dipping status in response to the HK diet
	High potassium diet (HK; n = 20)	*Mean age (year)* = 14 ± 1 (dippers); 14 ± 1 (nondippers)		
	80 mmol/d of potassium with 4 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	*Race* = 100 % African American		
	Usual diet control (CTL; n = 20)	Mean BP *(mmHg)* = 109 ± 63 mmHg (dippers); 112 ± 61 mmHg (nondippers)		
	Healthy diet program with weekly 1-h classes covering feedback on food record keeping and 24-h urine results			

Sorof et al. 1997 (United States) [96]	Three group crossover RCT;	*N = 39* (F = 33, M = 17)	*12-h Urinary potassium:* 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
	Duration = 1-week/condition	Children ages 7–15 recruited from schools and clinics with (*n* = 22) and without (*n* = 17) family history of essential HTN		Higher vegetable consumption in Caucasian children than in African American children was associated with higher urinary potassium/creatinine ratio
	Potassium solution 1.5 mmol/kg/day	*Mean age (year)* = 12		
	Placebo solution cherry syrup	*Race* = 44 % Caucasian; 56 % African American		
	CVR stressors blood sampling, cold pressor, video game			
Wilson et al. 1999 (United States) [36]	Two group RCT	*N* = 53 (F = 26, M = 27)	*24-h Urinary potassium:* Dietary K increase significantly over time in the HK group ($p < .02$) and K levels were significantly higher in the HK group versus the CTL group	At 3 weeks assessments all SS and SR participants in the HK group who had been nondippers (33 % and 6 % respectively) achieved dipping status due to decreased nighttime DBP
	Duration = 3 weeks/group	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 high sodium diet		Participants in the CTL group did not show decreases in night time DBP
	High potassium diet (HK; n = 26)	*Mean age (year)* = 14 ± 1 (SS); 14 ± 1 (SR)		Increased potassium intake did not affect weight or sleep duration
	80 mmol/d of K with 4 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			
	Usual diet control (CTL; n = 32)			
	Healthy diet program with weekly 1-h classes covering feedback on food record keeping and 24-h urine results			

(continued)

Table 15.1 (continued)

Authors	Intervention	Sample baseline demographics	Compliance	Findings
Wilson et al. 1999 (United States) [63]	Two group RCT	*N* = 58 (F = 30, M = 28)	*24-h Urinary potassium:* Dietary K increase significantly over time in the HK group ($p < .02$) and K levels were significantly higher in the HK group versus the CTL group	At 3 weeks assessments all SS and SR participants in the HK group who had been nondippers (33 % and 6 % respectively) achieved dipping status due to decreased nighttime DBP
	Duration = 3-weeks/group	Salt-sensitive (SS; *n* = 16) and salt resistant (SR; *n* = 42) African American adolescents. Salt sensitivity was defined as an increase in MBP ≥5 mmHg in transitioning from a low to high salt diet		Participants in the CTL group did not show decreases in night time DBP
	High potassium diet (HK; n = 26)	*Mean age (year)* = 14 ± 1 (SS); 14 ± 1 (SR)		Increased potassium intake did not affect weight or sleep duration
	80 mmol/d of K with 4 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	Mean BP (mmHg) = *103/58 (SS); 100/57 (SR)*		
	Usual diet control (CTL; n = 32)			
	Healthy diet program with weekly 1-h classes covering feedback on food record keeping and 24-h urine results			

Mu et al. 2005 (China) [126]	Two group RCT	*N* = 261 (F = 133, M = 128)	*Compliance not reported*	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 ($p < .01$) and was negatively correlated with increase in BP. Moderate increases in dietary calcium and potassium may promote urinary sodium excretion
	Duration = 2-years/group	School children in grades three and four with salt sensitivity (SS) and without salt sensitivity (NSS) from Hanzhong, China		
	Potassium and calcium supplementation (KC; n = 136)	*Mean age (year)* ~ 10.5		
	Children were instructed to take a tablet consisting of 10 mmol potassium and 10 mmol calcium daily	*Race* = 100 % Asian		
	Placebo control (CTL; n = 125)	*Mean BP (mmHg)* = 103/63 (SS/KC); 103/63 (NSS/KC); 103/63 (SS/CTL); 103/63 (NSS/CTL)		
	Children were instructed to take a placebo tablet that was identical in appearance and taste to the potassium and calcium tablet			
	All participants were instructed to maintain usual sodium intake			
Sodium and potassium interventions				
Sinaiko et al. 1993 (United States) [12]	Three group RCT	*N* = 210 (F = 105, M = 105)	*24-h UNa:* LS group did not achieve 70 mmol/day goal; no change in boys Na excretion (non-compliance); reduced Na excretion in girls from baseline	No between group differences were found for boys and BP increased over time
	Duration = 3-years/group	Minneapolis, MN public school students in grades 5–8 with SBP >109 mmHg (boys) and 108 mmHG (girls)	Percentage of expected capsule use: *Potassium capsule* 84.2 %, range = 77–93 %	For girls in sodium and potassium interventions BP increased less over time than for placebo groups but did not significantly decrease
	Low sodium diet (LS; n = 70)	*Mean age (year)* = 13.2 ± 0.1	*Placebo capsule* 91 %, range = 85–97 %	Differences between boys and girls may be due to poorer compliance in boys
	70 mmol/day + nutrition counseling seven times during mos. 1–3 and then tri-monthly. Phone calls were made to reinforce instructions	*Race* = 86.5 % Caucasian; 13.5 % African American		Poor compliance in the LS group challenges the feasibility of long-term sodium reduction in adolescents
	Potassium capsule (K; n = 71)	*Mean BP (mmHg)* = 114/63 (LS); 114/67 (K); 114/65 (CTL)		
	1 mmol/kg/day, double-blind			
	Placebo capsule (CTL; n = 69)			
	Identical to potassium, double-blind			

(continued)

Table 15.1 (continued)

Authors	Intervention	Sample baseline demographics	Compliance	Findings
Günther et al. 2009 (United States) [93]	Cross-sectional study	*N* = 2830 (F = 54 %, M = 46 %)	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
	Type 1 diabetes (T1D; n = 2440)	Participants in the SEARCH for diabetes in youth trial ages 10–22 with type 1 or type 2 diabetes		
	Type 2 diabetes (T2D; n = 390)	*Mean Age (year)* = 14.7–16.6		
	All participants' diets were analyzed and assessed for concurrence with 8 food groups of the Dietary Approaches to Stop Hypertension (DASH) diet for increased fruit and vegetable intake	*Race* = >71 % Caucasian; >5 % African American; >11 % Hispanic *Race T2D* = >20 % Caucasian; >30 % African American; >14 % Hispanic; >12 % Native American		
		Mean BP (mmHg) = 108/68		
Mu et al. 2009 (People's Republic of China) [57]	Three group RCT	*N* = 325 (F = 152, M = 173)	*24-h UNa:* 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
	Duration = 3-years/group	Chinese adolescents from northwest China with SBP >90th percentile by age and sex		Using a salt substitute which contains potassium and calcium may be as effective at reducing BP as sodium restriction
	Low sodium diet (LS; n = 110)	*Mean age (year)* = 20 ± 3.5		
	Health behavior education given until salt intake decreased to 50–100 mmol per person	*Race* = 100 % Chinese		
	Potassium + calcium capsule (K+Ca; n = 101*)* families given supplement and asked to eat as usual	*Mean BP (mmHg)* = 122/75 (LS); 124/75 (K+Ca); 124/77 (CTL)		
	Control (CTL; n = 114) families asked to eat as usual			

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

potassium chloride supplementation (1 mmol/kg potassium chloride/d), a low-sodium diet (70 mmol sodium/d), or a placebo (normal diet plus placebo capsule). The results demonstrated that both the potassium supplementation and sodium restriction interventions were effective in reducing the rise of casual BP in girls, but not in boys. Consequently, the feasibility of long-term restriction of dietary sodium in boys may be limited.

In a study by Couch et al. [49], the Dietary Approaches to Stop Hypertension (DASH) diet [92] 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 recent study, Günther and colleagues reported that youth with type 1 diabetes who demonstrated adherence to the DASH diet showed an inverse relationship with hypertension, independent of demographic, clinical, and behavioral characteristics 93. Note, however, that in the Günther et al. study, adherence to the DASH diet was not associated with such reductions in the risk of hypertension among youth with type 2 diabetes. Taken together, these studies suggest that 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 indicates that dietary electrolyte intake plays an influential role in circulatory responses to stress. Falkner and colleagues have conducted a number of investigations evaluating how altering dietary sodium affects CVR [94]. One study 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. The girls with a positive family history of primary HTN showed an increase in resting baseline and stress BP levels. The girls with a negative family history did not. These findings have been replicated in young adults [95]. However, for those with a positive family history of primary HTN, changes from baseline to stress were similar before and after salt loading.

Sorof et al. examined whether CVR was inversely related to the dietary intake of potassium in 39 children [96]. At baseline, the 24-h urinary potassium/creatinine ratio varied inversely with diastolic CVR in Caucasian children (who had a positive family history of HTN); however, CVR was not attenuated by potassium supplementation (1.5 mmol/kg/d of potassium citrate) compared to placebo. Urinary potassium/creatinine ratio was higher in Caucasian children than in African-American children and dietary potassium-modulated CVR in Caucasian children with a family history of HTN.

Consistent with this finding, we demonstrated no significant change in BP reactivity in African-American adolescents who complied with a 3-week high-potassium diet [36]. This study examined the effects of increasing dietary potassium on BP non-dipping status in salt-sensitive and salt-resistant African-American adolescents. Urinary potassium excretion significantly increased in the treatment group (35 ± 7–57 ± 21 mmol/24 h). At baseline, a significantly greater percentage of salt-sensitive (44 %) subjects were non-dippers based on diastolic BP classifications ($p < 0.04$), compared to salt-resistant (7 %) subjects. After the diet intervention, all of the salt-sensitive subjects in the high-potassium group achieved a dipper BP status due to a drop in nocturnal diastolic BP (daytime 69 ± 5 vs. 67 ± 5; nighttime 69 ± 5 vs. 57 ± 6 mmHg). These results suggest that a positive relationship between dietary potassium intake and BP modulation can prevail, although daytime BP may be unchanged by a high-potassium diet. Our data are the first to indicate that increasing dietary potassium reversed non-dipping status in salt-sensitive subjects, while having no effect on daytime BP. These findings in part corroborate other

investigations that have shown beneficial effects of increasing potassium on BP responses in salt-sensitive populations.

For example, Fujita and Ando demonstrated that salt-sensitive hypertensives 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 [97]. Svetkey et al. 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 [98]. 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 which restricted sodium intake, 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 [57].

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 [13, 78, 99]. The mechanisms underlying BP non-dipping status are unknown. One potential mechanism by which potassium may alter nighttime BP may involve potassium-related natriuresis [100, 101]. Restricting potassium intake leads to 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 [78]. If non-dippers are characterized by excess SNS activity and increased peripheral resistance during sleep, this potassium-mediated vasodilatory effect could explain the reversal of non-dipping status in our prior study [36]. Other studies that support this hypothesis show that intra-brachial arterial infusions of potassium chloride increase forearm blood flow and decrease forearm vascular resistance in healthy adults [102, 103]. Potassium supplementation given in combination with a high-sodium diet also suppresses the increase in catecholamine responses typically seen in response to salt loading [104]. Previous studies have shown that total peripheral resistance and norepinephrine responses to stress are greater in offspring of hypertensives than in normotensives [105]. Several adult studies have also confirmed that SNS activation occurs in individuals with elevated nighttime BP [106]. In summary, these data support the hypothesis that the SNS may have a controlling influence on non-dipping BP status.

Nutrition and Dietary Compliance in Youth

Several lines of evidence suggest that targeting families may be important for promoting healthy dietary compliance in children and adolescents. Previous research has demonstrated moderate aggregation of dietary variables among adolescents and their parents [107]. Furthermore, because families 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 [108].

Social support from family members may be one way that parental involvement influence compliance with 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 examined the relationship between gender, dietary social support (emotional), and compliance to a low-sodium diet [109]. 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 [UnaV] < 50 mEq/24 h) reported higher levels of dietary support from family members than boys who were compliant (UnaV < 50 mEq/24 h). In contrast, boys who were compliant reported lower levels of dietary support from family members than boys who were noncompliant.

In a study by Nader et al. [110], Caucasian, African-American, and Mexican-American families were randomly assigned to a 3-months 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' compliance with healthy dietary programs that could ultimately decrease the risk of HTN and cardiovascular complications.

Another way that parents, teachers, and peers may influence adolescents' compliance with healthy eating habits is through role modeling. Cohen, Felix, and Brownell randomly assigned adolescents to either peer-led or parent-led promotions of a low-sodium, low-fat dietary intervention [111]. 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., 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 [112]. 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 [113]. 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 compliance to sodium restriction and dietary potassium supplementation. Sinaiko et al. reported urinary electrolyte excretion data over the course of a 3-year intervention in fifth through eighth graders [12]. Boys were less likely to comply with a sodium restriction of 70 mmol/d than girls. Subsequently, BP effects were only significant for girls. In a study by Wilson et al. [114], boys were more likely than girls to comply with a 3-week dietary intervention of increasing potassium to 80 mmol/d intake. 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. 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.

Conclusions and Implications for Future Research

In summary, the profile of elevated cardiovascular risk includes BP parameters such as high casual BP, elevated CVR, and ambulatory BP non-dipping status. While much of the research to date has focused on adult populations, national efforts are continuing to move in the direction of prevention at the childhood level [16].

Reducing sodium and increasing potassium intake effective approaches for reducing the risk and development of HTN, yet much work remains to be done among children and adolescent

populations. Research by our group suggests that compliance to high-potassium dietary interventions may be easier than low-sodium diets. This chapter provides the basis for promoting effective nutritional-electrolyte-focused interventions. However, other important factors must be considered, including those related to obesity and sedentary lifestyles. Minority populations, African-Americans, are at high risk for developing HTN in early adulthood, and efforts should focus on preventing HTN in these communities. Continued efforts will be needed to assure prevention of obesity in underserved and minority youth. Abnormal SNS activity may be linked to the elevated BP parameters reviewed in this chapter. The role of dietary intake on BP markers suggests that further attention should be paid to promoting positive dietary lifestyle skills in youth. Promoting healthy diets that target decreasing sodium and increasing potassium may help to decrease SNS activation. The precise physiological mechanisms that underlie the observations reported in this chapter should be another focus of future investigations.

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Ethnic Differences in Childhood Blood Pressure

16

Joshua Samuels, Xamayta Negroni-Balasquide, and Cynthia Bell

Abstract

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 body height. The current threshold values ignore any ethnic differences in childhood blood pressure. While young children likely have no differences in BP related to ethnicity, emerging data suggest that, at least in older children, race and ethnicity may be important factors influencing blood pressure. 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

Ethnic • Race • Minority • Children • Hypertension • ABPM

Introduction

Blood pressure (BP) differences between various ethnic groups are well described in the adult population [1]. Large, cross-sectional studies have demonstrated that, per capita, minority ethnic groups have both a higher prevalence of hypertension (HTN) and more significant end-organ damage and outcomes [2, 3]. Although a growing body of evidence indicates that differences in blood pressure parameters appear during adolescence [4–6], the cause of these differences and when they develop in childhood is yet to be fully determined.

Adults

Worldwide, Blacks not only have the highest prevalence of hypertension but also have more severe HTN, more hypertensive target organ damage, and perhaps an earlier onset of HTN. These findings are certainly true of Blacks in the United States. The National Health and Nutrition Examination Survey (NHANES) has consistently demonstrated that non-Hispanic Blacks in the

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United States have a higher prevalence of essential hypertension, particularly severe hypertension (>180/100 mmHg) which is over eight times more prevalent in Blacks than in other ethnic groups [2]. The American Heart Association 2009 report notes that Blacks in America continue to be at increasing risk for essential hypertension [7]. Worse, the CDC continues to dispense a poor report card on the control of hypertension in the United States, with fewer than half of patients adequately treated to target blood pressures [8]. Although poorly controlled HTN is rampant across all segments of society, the most recent MMWR reports that Blacks (57.0 %) and Hispanics (63.1 %) are significantly more likely to have uncontrolled HTN than their White (51.5 %) counterparts ($p < 0.001$).

Do Racial Differences in Blood Pressure Begin in Children

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 Fourth Report, offer separate normative values for children of varying ethnic backgrounds [9]. Though height, age, and gender all are accounted for in the determination of pediatric normative BP values, ethnicity is not included.

Rosner and colleagues have analyzed the Pediatric Task Force data used to generate the pediatric normative BP values on several occasions to assess whether ethnicity is a factor influencing BP [10]. Their initial analysis [7] included 47,196 children aged 5–17, including 29,730 White and 17,466 Black subjects. The only racial differences found were elevated BP in obese White males versus obese Black males and normal weight Black males versus normal weight 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 from the Pediatric Task Force, 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 [6]. 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 Pediatric Task Force data, Daniels in 1996 showed significant differences in BP between 9- and 10-year-old Black girls compared to Whites [11]. The 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 [4]. 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. 16.1) [4]. 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 third National Health and Nutrition Examination Survey (NHANES III) data, gathered between 1988–1994 and 1999–2000, to assess trends in BP among US children and teens aged 8–17 years [12]. 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).

Munter's analysis is not the only study that suggests that ethnic differences in BP might differ between boys and girls. In the United Kingdom, Harding and colleagues followed a multiethnic population of 6,643 teens in the Determinants of Adolescent Social Well-Being and Health (DASH) study [13, 14]. Although children self-reporting as of Black African origin (distinguished in their

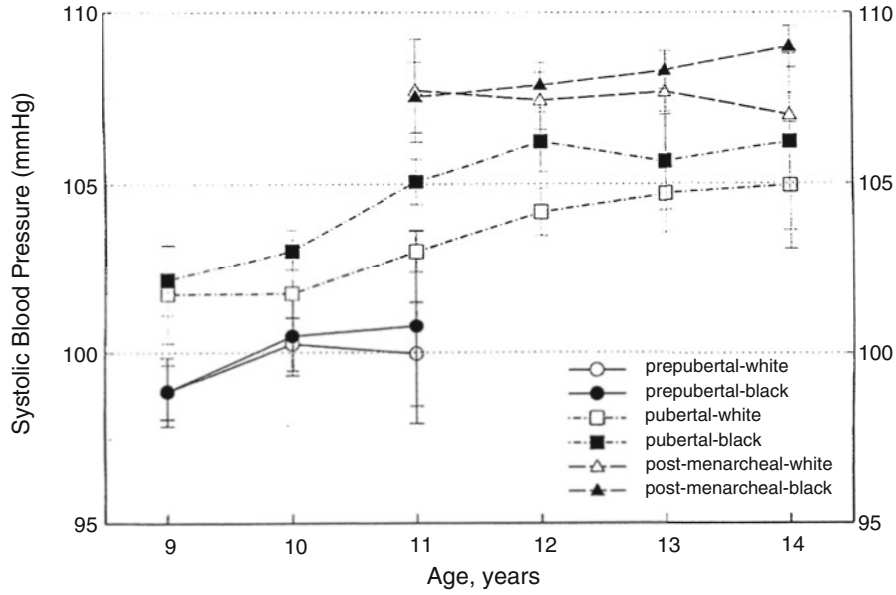

Fig. 16.1 Mean systolic blood pressure (mmHg) by age, sexual maturation stage, and race (From Daniels (1998) Hypertension 31:101 [4] with permission)

cohort from Black Caribbean subjects) were more overweight and more socioeconomically disadvantaged, Harding reports no initial difference in BP in early adolescence[14]. At age 12, systolic BP 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 [15]. 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 the White girls. Diastolic pressure 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. 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 [16]. Most studies including Asian children have found either no significant differences in BP in Asian children compared to White counterparts or have found a lower risk of HTN compared to other ethnic groups.

Houston-based blood pressure screening has been ongoing since 1978. Early cohorts were included in the Pediatric Task Force data [17]. More recently school-based screening studies have continued to gather information on blood pressure and now include over 20,000 children aged 10–19 years. Overall prevalence of HTN in these children is 1.6 % in Asians, 2.5 % in Whites, 2.7 % in Blacks, and 3.1 % in Hispanics. Absolute systolic blood pressure, as measured by BP index, is significantly higher in Hispanics than in all other ethnic groups.

Hispanics and Ethnic Differences in BP

Most discussions of racial or ethnic differences in blood pressure have focused on non-Hispanic Blacks and 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, Hispanics in the United States were a median of only 27.6 years old compared to 42.3 years in non-Hispanic Whites [18]. 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 have yet to reach the typical older age of HTN onset. Recent NHANES adult data show Black males to have the highest prevalence of HTN at 37.8 %, while Hispanics and Whites have similar rates of 22.1 % and 26 %, respectively. Additionally, HTN prevalence has increased from 1998 to 2008 in adults for all racial groups except for Hispanics [2, 19]. Despite similar rates of HTN, effective control of HTN in Hispanics, particularly young Hispanics, is often the lowest out of all ethnic groups. Recent national studies have shown that Hispanics aged 20–39 have the lowest knowledge of, therapy for, and control of their HTN [2, 20]. 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 HTN in Hispanics can be uncovered. These analyses will provide insight into the forthcoming HTN 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 [21]. With the rising proportion of Hispanics in the young population, recent studies in children have shown that Hispanic youths have an increased prevalence of HTN compared to non-Hispanic White youths 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 [22]. 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 [23]. 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 [6].

Our data from the UT-Houston screening program over the last 12 years has shown the highest rate of HTN among adolescent, obese, Hispanic boys at 10.5 % [24]. This trend is consistent with our concurrent finding that Hispanic boys of all ages have the highest rate of obesity at 27.8 % compared to either Black (20.2 %) or White boys (16.2 %). These higher rates of obesity might largely explain the emerging trend of increased HTN in Hispanics.

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 % [25, 26].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) [27]. 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 [28–31], other factors may also play a role in the development of early HTN.

Origins of Ethnic and Racial Differences

As in adults, the predominant diagnosis in teens with elevated blood pressure is essential hypertension. While deemed essential 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 ethnicities 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 US Department of Health and Human Services reported that from 1988 to 1994 the prevalence of HTN was 26–27 % for poor or near poor men while only 22 % in men from more affluent background [7]. 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.

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 [7, 32]. 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 HTN than those from Chicago or Oakland, although within Birmingham, Blacks continued to have higher BP than Whites [33]. 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 [34]. 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 [35].

Diet is another important factor in blood pressure regulation that varies across both SES and ethnic groups. The Treatment of Mild Hypertension Study (TOMHS) [36] assessed baseline dietary sodium intake by measuring urinary excretion of Na^+ and Na^+:K^+ ratio. The study reported that discrepant levels between Blacks and Whites correlated with differences in SES [37]. Specifically, higher urinary Na excretion was found in Blacks at lower SES and education, but not Whites [38]. 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 Blacks had severely diminished SBP dipping at baseline compared to Whites, no ethnic differences in SBP dipping were found following the DASH diet intervention [39]. 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 non-dippers (<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 [40].

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 blood pressure 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 [41]. Additionally, subjects with the highest blood pressure were those with the highest "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 [42]. 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 [43].

Much effort has gone into establishing the mechanism of essential 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 [44]. 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 [45, 46]. When 118 Black youth were physiologically challenged, they had a greater increase in BP and a more delayed return of BP to pre-stress 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.

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 [47–51]. 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 [9, 52]. There is emerging evidence that, like other measurements of BP, ambulatory BP patterns differ between ethnicities. A meta-analysis in adults has shown elevated ambulatory SBP and DBP during both days and nights in Blacks compared to Whites [53].

Most studies in children have also found evidence that ABP varies by race. A particularly common finding is reduced dipping, a blunted nocturnal decline in BP from wake to sleep, 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 [54]. 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 ABP 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 [55].

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 [56]. In a study that spanned childhood through young adulthood, Wang measured a 24-h ABP 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 [5].

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 groups and genders. One of the first studies showing racial 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 [57].

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 [58]. 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 [59]. These differences between bone age and chronologic age were more pronounced with increasing blood pressure stages.

Aguilar studied ABPM results in 43 clinically normotensive, obese children aged 7–17 years and showed that multiple ABP measures correlated to BMI z-score but not to race [60]. 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 [61]. 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 [26].

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 ABP normative thresholds are based on a cohort of exclusively White, European children that did not include any ethnic variation [62, 63]. Despite the ethnic and racial differences in BP and target organ damages described in this chapter, minority children were completely unrepresented in establishing ABP normative thresholds. ABP 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 National High Blood Pressure Education Program's Fourth Report (FR) to standardize ABP values collected in a multiethnic population [9, 64]. Brady controlled for gender, age, and height by dividing ABP means by FR 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 ABP thresholds are the levels that predict hypertensive target organ damage. Though these exact thresholds are unknown, it is clear that children with HTN based on current thresholds do develop target organ damage [65].

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 organ damage (EOD), and cardiovascular events [2], data on the effect of hypertension on target organ damage are less clear in minority children. There is some data suggesting that childhood hypertension is in fact related to premature death, at least in some ethnic populations such as Native Americans [66]. The most

common EOD found in children with HTN is left ventricular hypertrophy (LVH) [9, 65, 67–69].

Twenty-five years ago, Burke showed an association between systolic blood pressure, body surface area, and left ventricular size among subjects 7–22 years old. The study did not uncover racial differences in cardiac anatomy [70]. 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 [71]. In a study showing that lean body mass, fat mass, and BP all affect left ventricular mass, Daniels found significant race and gender interactions. While lean body mass was the most important factor contributing to LV mass, DBP was associated with LV mass in Whites but not Blacks[72]. Dekkers studied 687 subjects between ages 7 and 27 with up to 10 repeated echocardiograms [73]. 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 too have demonstrated both ethnic and gender differences in LV mass indexed to height 2.7 (in order to standardize LV mass based on body size). Harshfield showed that the higher nocturnal SBP in Black adolescents was also associated with greater LV mass index on two separate visits [55]. 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 [61]. This study found that Black youths had higher baseline LVM index, resting SBP, and relative wall thickness that could be related to findings at subsequent visits of increased BP, left ventricular mass, and lower mid-wall fractional shortening in Blacks compared to Whites. Recently, Falkner and colleagues have shown in a cohort of Black adolescents that both obesity and HTN are significantly associated with increased left ventricular mass index [74, 75]. 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. This result suggests that obesity, and not race or BP elevation, could play a bigger role in the development of LVH [64]. 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 [76].

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 [77, 78]. 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 [1–3]. Despite these efforts, Blacks and Hispanics still fall far behind Whites in control of BP to adequate targets [8]. The residual HTN 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 EH, 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 [78]. 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 [79]. 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 responded, across all trials Blacks failed to demonstrate a significant response. Memon further showed that

Blacks receiving fosinopril required a higher dose to achieve adequate SBP control [80]. Similarly, Hazan studied the blood pressure-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 [81].

Conclusion

As has been shown consistently in adult populations, studies suggest that blood pressure values are not equal across racial and ethnic groups in childhood. Blacks, and likely Hispanics too, demonstrate higher blood pressure 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. The mechanisms of the differences are not completely clear, and further examination is ongoing into the underlying causes of racial and ethnic disparity in blood pressure. Despite differences in blood pressure findings across racial and ethnic groups, current National High Blood Pressure Education Program guidelines do not take these factors into account in either the diagnosis or management of elevated blood pressure in youths. As additional data are gathered, future guidelines might consider whether racial and ethnic differences are significant enough to warrant disparate approaches in minority children.

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Childhood Obesity and Blood Pressure Regulation

17

Donald L. Batisky

Abstract

Obesity in children and adolescents continues to occur with increasing frequency and has been associated with the development of clinical consequences of obesity such as hypertension. This chapter will begin with a review of the definitions of hypertension and prehypertension in children and adolescents, followed by discussion of 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.

Keywords

Obesity • BMI • Prehypertension • Hypertension

Introduction

Obesity in children and adolescents continues to occur with increasing frequency and is now the most common nutritional problem noted in developed countries. It has been associated with clinical outcomes that have been typically felt to be more likely to be diseases of adults. With the increased levels of obesity, a number of complications may arise, and hypertension is one of them. Some of the other complications 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.

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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 to accomplish.

Earlier editions of this textbook included comprehensive reviews of this topic by Rocchini which offer extensive background information that remains pertinent today [1, 2].

Background and Definitions

Hypertension may be defined a number of ways. Clinically it can be defined as the sustained level of 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. 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. According to this approach, BPs that fall above the 95th percentile for age, gender, and stature on at least three occasions would classify a patient as hypertensive [3]. In addition to defining hypertension as BP being >95th percentile, the National High BP Education Program has proposed a staging of hypertension: stage 1 HTN, BP 95th–99th percentile plus 5 mmHg, and stage 2 HTN, >99th percentile plus 5 mmHg [3]. Prehypertension (pre-HTN) has been defined as BP values falling between the 90th and 95th percentiles on a consistent basis or >120/80 for adolescents.

Presently there is no direct evidence linking the stratifications of prehypertension and 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 [4]. 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. Conversely, a recent 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 [5].

Prehypertension is also seen in obese children and adolescents. This is a stage at which one might feel that preventive strategies could be most likely to help. Effective interventions when one is prehypertensive might allow for alleviation of manageable risk before the 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 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 [6].

In recent years, there has been more attention paid to assessing body mass index (BMI) in children and adolescents. A child is considered overweight when BMI is >85th percentile and obese when BMI is >95th percentile. 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. For further discussion of hypertension in the MetS, please see Chap. 19.

Epidemiology

Surveys examining large groups of children from the middle part of the last century forward have shown clearly that the prevalence of overweight 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 [7]. Among physicians taking care of children and adolescents with elevated BP, there is a feeling that the link between obesity and BP has led to more children being identified with high BP and diagnosed with HTN, yet the epidemiologic data are somewhat conflicting [8–16]. 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 definite conclusion is difficult for a number of reasons, including 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 consistent definition of elevated BP in children across these studies.

In addition to the changes in prevalence, there is noted an alarming rate of progression and tracking of elevated BP from childhood into adulthood. 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 [17]. Additionally, Redwine and colleagues noted the increased risk for developing hypertension during adolescence, with a rate of 1.1 % per year [18]. 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 [19]. A recent 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, noninstitutionalized population. In the survey done between 1999 and 2008, over 3,000 participants were aged 12–19 years. In that sample, there was a prevalence of 14 % for prehypertension/hypertension [20].

So, it is quite clear over the past four to five decades that overweight status and obesity are more common and with that comes substantial additional cardiovascular risk.

The Relationship Between Obesity and Hypertension

A number of studies done over the past two decades have reported on 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 [21–26]. 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. Odds ratios for hypertension in that study ranged from 2.5 to 3.7 [27].

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 2,000 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 [28].

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 nonobese subjects [26]. While it seems simple to classify a patient by weight status as "obese" or "nonobese" in determining the risk of hypertension, it is important to note that there is not a 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 percentile. 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 [29].

Chandramohan et al. [30] recently reported on an interesting finding in obese children in the NHANES cohort from 1988 to 1994. In a retrospective analysis of 4,667 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, and 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 importance 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 [7]. 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 [31].

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 the 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 [32–34]. 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 5,000 children were in the first cohort, and almost 8,000 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, their findings clearly have implications for accurate BP measurement [35].

Mechanisms of Hypertension in Obesity

A number of mechanisms have been studied and proposed to link obesity and hypertension. While the exact pathophysiologic mechanism that links obesity and hypertension is still unknown, it is likely to be complicated, multifactorial, and variable. Several mechanisms are likely called into play to intertwine the pathophysiology of obesity with that of hypertension. Some of the more likely mechanisms are listed in Table 17.1.

Table 17.1 Mechanisms of hypertension in the overweight/obese patient

Insulin resistance
Sympathetic nervous system activation
Renin-angiotensin-aldosterone system alterations
Leptin resistance
Vascular reactivity alterations
Hypothalamic-pituitary-adrenal axis alterations

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 of 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 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 [7].

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 [36], and a hyperdynamic cardiovascular state was positively associated with several measures of obesity [37]. 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 nonobese 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 nonobese adolescents [19]. Rocchini et al. found that weight loss, with or without exercise, resulted in a significant reduction in heart rate in obese adolescents [38].

It has also been reported that obese children have increased heart rate variability and BP variability when compared with nonobese children [26, 31]. 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 [40]. Furthermore, physical training in obese children appears to alter autonomic function by reducing the ratio of sympathetic to parasympathetic activity [41]. 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. Several studies have reported positive associations between fasting insulin levels and resting BP in obese children and young adults [7, 42–47]. Nonetheless, this association does not necessarily indicate causation. Lughetti et al. [48] 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 [38, 49] and to render previously salt-sensitive individuals insensitive to the hypertensive effects of salt loading [38]. Based on these data, it has been suggested that the insulin resistance associated with obesity may prevent insulin-induced glucose uptake but leave the renal sodium retention effects of insulin relatively preserved, thereby resulting in chronic volume overload and maintenance of BP elevation. However, Csabi et al. [50] 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 [51, 52] and children with familial hypercholesterolemia [53–55] compared with normal controls. In addition, decreased vascular compliance has been reported in diabetic children [56] and children with familial hypercholesterolemia [57]. 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. [58] reported lower 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, [59] which was improved after weight loss [60].

Insulin resistance and hyperinsulinemia are activators of the renal sympathetic nervous system, 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).

Another hormone that is produced by adipose tissue is leptin. Higher levels of leptin are associated with elevated BP, and that relationship is mediated by BMI and effects on the sympathetic nervous system [61]. Obese individuals have also been shown to produce less adiponectin, which is an antiatherogenic, cardioprotective hormone that is secreted by adipocytes. Levels of this hormone are inversely correlated with BP in obese children and adolescents [62]. 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. 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 [63]. Weight loss can reduce sympathetic overactivity in obese patients and that may partially explain the lower BP noted in response to dieting [64]. Central fat distribution is associated with disturbances in the hypothalamic-pituitary-adrenal axis, and an axis that is disrupted may be implicated in the development of the metabolic syndrome [65].

Although these data have provided insight into the potential mechanisms of obesity hypertension in children, truly mechanistic studies to illustrate 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 one considers treatment of hypertension in any patient, one must consider potential etiologies, as it is often most effective to manage an illness or condition by treating the underlying disorder. That is often not so easy to do in the area of hypertension associated with obesity as there may be a number of interacting features. There are generally two general approaches to treatment. One broad area is that of non-pharmacologic management, referred to as Therapeutic Lifestyle Changes (TLC) in the Fourth Report, and the other 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 17.2 displays elements of a comprehensive treatment plan to consider. It is generally accepted that patients with pre-HTN without evidence of target organ disease should be initially 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.

Table 17.2 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	

Lifestyle Changes: Weight Loss and Exercise

The Fourth Report lists diet, exercise, and weight loss as potential lifestyle changes. Since weight loss, involvement in aerobic exercise, and modifications of the diet have been shown to reduce BP in children and adolescents, it seems reasonable to believe that these approaches should be considered the primary treatment of hypertension when the hypertension is related to obesity. 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. [66] 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. [67] 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 studied three interventions in a randomized, controlled trial over a 20-week period: 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 is maintained.

Figueroa-Colon et al. [68] 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. [49] 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. Similarly, Gallistl et al. [69] 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.

Although these studies suggest that BP reductions are induced by weight loss in obese children, each is limited by the absence of a matched control group to show that the BP reduction was *directly* attributable to weight loss.

Weight loss not only reduces BP but it may also improve some of the other cardiovascular risk factors that cluster with the 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. When HTN is affecting the obese child or adolescent, one cannot overlook that obesity is a part of the complex equation necessary for optimal management of the patient. Another important issue to consider when dealing with the obese child or adolescent is that obesity is often a family problem, and treatment will require buy-in from the family to be successful. The types of exercise felt to be most beneficial are aerobic forms 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 [[3]]. It is also important to consider giving children and families some very concrete guidelines, 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 [70]. 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. Finally, while exercise training has also been shown to reduce BP for a limited period of time, on the order of 3–6 months, once the exercise ends, it seems that BP returns to pretreatment levels [71, 72].

Lifestyle Changes: Dietary Interventions

It is very important to consider dietary strategies in this setting of obesity-associated 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. Within the spectrum of therapeutic lifestyle changes (non-pharmacologic management strategies), dietary interventions have been studied most often.

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.

While dietary advice is recommended as first-line therapy, there really is little evidence that it works. In a recent [73] 2-year trial of potassium and calcium dietary supplementation in Chinese children who had salt-sensitive hypertension, improvement in systolic BP was observed. Relative to obesity in general, there are many studies showing that diet, exercise, and behavior modification can lead to improvement for children; however, there is also a high rate of recidivism.

When looking more specifically at children with HTN, one can see that a few studies have looked at diet as a modifiable element of a child's life that can result in improvement. 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 [74].

The DASH diet, which stands for Dietary Approaches to Stop Hypertension (www.dashdiet.org), 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 nonfat 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.

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 [75].

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 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 biweekly phone calls by a trained interventionist, and four biweekly 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 a 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 [76].

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.

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 [77], such success has not been uniform. This management approach is very labor intensive and is often not covered by medical insurance [78]. Other dietary approaches which have been tried include the very low-calorie diet [79] and the protein-modified fast [80]. Although these dietary approaches can be effective in selected patients, they have also been associated with important adverse effects. Surgical approaches have been used in morbidly obese adolescents but are clearly not appropriate for a large number of patients.

Pharmacologic Considerations: Antiobesity Drugs

The role of pharmacologic management in the management of pediatric obesity has been controversial. The history of pharmacologic 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 pharmacologic therapy of obesity [81], with orlistat being the only agent with FDA approval for use in the pediatric age group. Sibutramine, an inhibitor of the reuptake of serotonin and norepinephrine, did have pediatric approval but has recently been withdrawn from the US market at the direction of the FDA.

Orlistat is a gastrointestinal lipase inhibitor that may hold promise for safe and effective pharmacologic treatment for childhood obesity. A 1-year placebo-controlled trial in which orlistat was used along with a hypocaloric diet, exercise, and behavior therapy showed a significant decrease in BMI among obese American adolescents [82].

Very 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^2 or greater (obese), or 27 kg/m^2 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 (phentermine and topiramate extended-release) is the first FDA-approved once daily combination therapy and the first new medication available in over a decade for the treatment of obesity. Belviq (lorcaserin) is a selective agonist of the serotonin (5-hydroxytryptamine) 2C (5-HT 2C) receptor. Both of them reduce appetite and may induce a negative energy balance. These medications have not yet been studied in children or adolescents [83].

Pharmacologic Considerations: Antihypertensive Medications

Pharmacologic therapy of hypertension in the setting of obesity needs to be considered as well. While one should not abandon lifestyle changes to use pharmacologic therapy, it is important to think of medication as adjunctive therapy while continuing to encourage weight reduction and other lifestyle changes 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, and 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 in Chapter 36, 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, yet they may also increase sympathetic nervous system (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 (ARBs) 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 [84].

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 at 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 [85]. Clinical experience and other approaches discussed here will continue to guide treatment of hypertension in younger obese patients [86].

Conclusions

Treating 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.

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Stress and Salt Sensitivity in Childhood Hypertension

18

Coral D. Hanevold and Gregory A. Harshfield

Abstract

The pressure response to sodium is heterogeneous among individuals with normal blood pressure and in hypertensives. Nevertheless, sodium restriction is typically recommended for everyone with hypertension. As reviewed here, categorization of an individual 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. We discuss an alternative way to administer a sodium load through stress exposure. Animal and human studies have demonstrated significant sodium retention during and after stress which in effect generates positive sodium balance and thus delivers a sodium load. Individuals demonstrating this response develop a volume-dependent elevation of the blood pressure. Similar to findings in salt-sensitive populations, target organ changes have also been associated with impaired sodium handling during stress. This pattern of sodium retention in response to stress has been improved or reversed after treatment with antihypertensive medications that block the renin-angiotensin-aldosterone system. 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 • Blood pressure • Stress • Pressure natriuresis • Sympathetic nervous system • Renin-angiotensin-aldosterone system

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Abbreviations

BP	Blood pressure
GFR	Glomerular filtration rate
GRK4	G protein-coupled receptor kinase 4
RAAS	Renin-angiotensin-aldosterone system
SNS	Sympathetic nervous system

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Relationship Between Salt Intake and Blood Pressure

A positive association between sodium intake and blood pressure (BP) levels has been demonstrated in many animal and human studies [1–3]. One of the key animal studies compared BP in 12 chimpanzees that were fed a diet that progressively increased in sodium content over several weeks with ten chimps fed their regular, low-sodium, diet [4]. Animals fed the high-salt diet demonstrated increasing BP which returned to baseline when the sodium intake returned to normal [4]. Human population studies have shown that individuals fed a higher-salt diet demonstrate higher blood pressures than those consuming a modest intake [1]. This point was confirmed in the INTERSALT cross-sectional study conducted in the 1980s of 10,000 adults in 32 countries [5]. These investigators demonstrated a positive independent relationship between 24-h urine sodium excretion and systolic BP. A high-sodium intake correlated with a rise in BP over time.

Similarly, in children a relationship between salt intake and BP was appreciated by He and MacGregor who evaluated cross-sectional data on 1,658 children and adolescents, 4–18 years of age, from the National Diet and Nutrition Survey conducted in 1997 in the United Kingdom [6]. 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. Recent examination of 2003–2008 NHANES data again confirmed a positive association between blood pressure and sodium intake [7]. Analysis of data on 6,235 US children and adolescents 8–18 years of age demonstrated a progressive rise in systolic BP with increasing sodium intake quartile with accentuation of this association in overweight/obese subjects. When individuals in the highest sodium intake quartile were compared to those in the lowest quartile, the odds ratio for high BP was 1.98 for the overall group but was 3.51 for overweight/obese subjects. Lastly, a relationship between sodium and BP has also been implied by the reduction in BP with salt restriction. He and MacGregor performed a meta-analysis of ten controlled pediatric trials and found significant lowering of systolic BP with a median reduction in salt intake of 42 % [2].

Key Role of Pressure Natriuresis

Abnormal sodium handling is a critical factor in the genesis of hypertension in populations characterized by a volume-dependent form of hypertension. In these individuals, the normal increase in sodium excretion in response to a rise in BP fails to occur. This key mechanism referred to as "pressure natriuresis" was elucidated in landmark studies in the 1970s by Guyton [8]. Guyton demonstrated that a rise in BP leads to a reflex increase in sodium excretion allowing a return of the pressure to baseline. Some individuals show an exaggerated pressure response to salt loading and volume depletion. In these salt-sensitive individuals, the slope of the renal function curve is blunted as shown in Fig. 18.1 [9]. In contrast, the curve is shifted to the right in salt-resistant hypertension without a change in slope.

Mechanisms Generating Salt Sensitivity

Several different mechanisms can result in the phenotype of salt sensitivity. Reduced sodium filtration is seen with a decrease in glomerular filtration rate (GFR) and contributes to HTN in individuals with chronic kidney disease. However, this mechanism is not a likely factor for most individuals with essential hypertension as GFR is typically normal or near normal. Impaired sodium handling by the renal tubule has been frequently implicated 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 monogenetic disorders such as Liddle's syndrome (see Chap. 6) has led to an appreciation of the effect of defects in the functioning of the epithelial sodium channel or a heightened response to mineralocorticoids in the distal tubule. Although such monogenetic conditions are rare, subtle abnormalities in distal tubule sodium

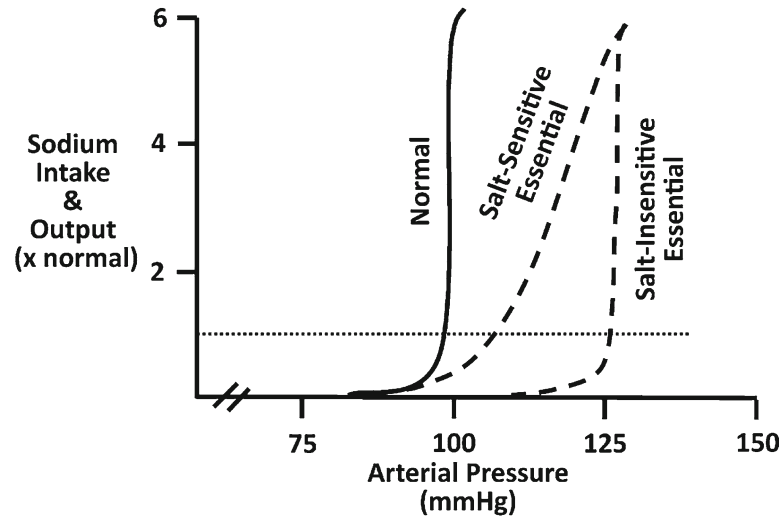

Fig. 18.1 Relationship between pressure and sodium intake (and output) in normals compared with salt-sensitive and salt-resistant individuals (Reprinted with permission [9])

reabsorption may prove to be involved in the pathogenesis of essential hypertension.

Additionally, attention has been directed at the importance of sodium handling in the proximal tubule, a site of action for angiotensin II and the sympathetic nervous system [10]. 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 [11]. Finally, Johnson et al. have suggested another important pathway to salt sensitivity is related to subtle microvascular injury leading to tubulointerstitial inflammation and fibrosis and eventually impaired renal tubular sodium handling [12]. Hyperuricemia has been implicated in initiating this process. Whatever the route to the phenotype, salt sensitivity is a complex phenomenon and likely dependent in most cases on the interaction of genetics, the environment, and physiological conditions.

Is Determination of Salt Sensitivity Important?

Classification of individuals as salt sensitive identifies them as being at greater risk for hypertensive target organ changes and cardiovascular morbidity than salt-resistant individuals. Bihorac et al. found increased frequency of hypertensive retinopathy, left ventricular hypertrophy, microalbuminuria, and higher serum creatinines in salt-sensitive hypertensive subjects as compared to salt-resistant hypertensives [13]. A greater risk for cardiovascular events has also been linked with salt sensitivity [14]. Furthermore, studies support the contention that long-term survival is influenced by salt sensitivity. Weinberger analyzed long-term data on normotensive and hypertensive adults previously evaluated and classified as salt sensitive or salt resistant [15]. Salt-sensitive hypertensives had the poorest survival of all groups. Interestingly, individuals who were normotensive but salt sensitive demonstrated similar survival to hypertensive subjects over time and significantly reduced survival compared to normotensive salt-resistant adults.

Additionally, from a practical standpoint 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 versus a calcium channel blocker [16]. Similar findings have been noted with other medications and non-pharmacologic interventions such as the DASH (Dietary Approaches to Stop Hypertension) diet and weight loss protocols

[17–20]. For example, the DASH diet was most effective in lowering BP when sodium intake was also restricted [17]. Thus, failure to consider salt sensitivity may compromise management of patients and cloud evaluation of the effectiveness of new antihypertensive medications across differing populations.

Salt-Sensitive Populations

As alluded to above, salt sensitivity is not universal. This phenomenon was demonstrated by Weinberger et al. who evaluated BP response to salt loading followed by volume depletion in 378 normotensive and 198 hypertensive human subjects [21]. Subjects were "loaded" with salt by infusion of 2 liters of 0.9 % normal saline intravenously over 2 h and fed a high-salt diet. The following day, volume depletion was induced with a restricted dietary sodium intake of 10 mEq in conjunction with furosemide 40 mg intravenously every 6 h for 3 doses. Salt sensitivity was defined by ≥10-mmHg difference in blood pressures obtained at completion of salt loading and volume depletion. Those demonstrating ≤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 restricted diet (<80 mEq of sodium/day) for 3 months [22]. For both normotensive and hypertensive groups, salt-sensitive individuals were more likely to be older than those who were salt resistant [21, 22].

Although older age is associated with salt sensitivity, 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 [23]. With salt sensitivity defined by a>5 % rise in mean arterial pressure, 31 % were identified as salt sensitive overall (41 % of normotensives and 23 % of hypertensives). Long-term studies by this group demonstrated an association between the BP response to oral sodium loading and change in BP over 5 years [24]. Further studies in pediatric and young adult populations have demonstrated that obesity, hyperinsulinemia, African-American race, family history of hypertension, and low birth weight are risk factors for salt sensitivity [23–28].

Identification of Salt-Sensitive Individuals

The heterogeneity of the response to sodium loading indicates a difference in sodium handling by the kidney in salt-sensitive versus salt-resistant individuals. At a given BP level, salt-sensitive individuals demonstrate reduced sodium excretion compared to those who are salt resistant. This tendency of salt-sensitive subjects to retain sodium was demonstrated in young adults by Faulkner and Kushner [23]. These investigators observed a negative correlation between sodium excretion and change in mean BP after oral sodium loading in the salt-sensitive subjects ($r=-0.28$, $p<0.01$). Similar findings have been reported by other investigators [21, 29, 30].

The complexity and subject burden of the protocols required to assess salt sensitivity described above have limited the clinical utility of establishing salt sensitivity [31, 32]. Identification of the salt-sensitive individual is most typically accomplished by demonstrating an increase in BP in response to sodium loading by the enteral or parenteral routes. A potential alternative method to demonstrate salt sensitivity involves taking advantage of the anti-natriuretic response to sympathetic nervous system (SNS) arousal to identify individuals who retain rather than excrete sodium during stress, referred to as stress-induced sodium retention or impaired stress-induced pressure natriuresis [33, 34]. The approach is based on rotating the axes of the pressure natriuresis curve discussed earlier, with sodium retention during stress (x-axis) leading to an increase in blood

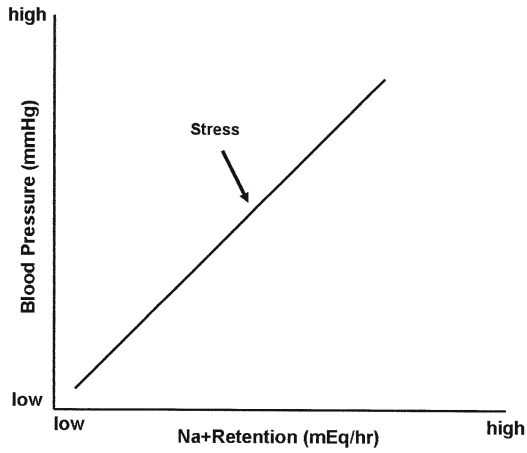

Fig. 18.2 Relationship between urine sodium retention and blood pressure during stress

pressure (y-axis). As shown in Fig. 18.2, the sodium load "delivered" by the kidneys increases with stress accompanied by a volume-mediated rise in blood pressure.

The primary evidence for this approach 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. Pioneered by Friedman, Koepke, and others, the focus of these studies was on the link between stress and hypertension [35–37]. The second is the efforts of DiBona and others to define the mechanisms through which SNS activation of the renal nerves can contribute to the development of hypertension in at-risk animals [38–40]. The intent of this line of research was characterization of the link between the SNS and the kidney. These studies demonstrated that hypertensive strains of rats retained sodium during stress. Further studies by additional investigators suggest that the antinatriuretic actions of stress-induced efferent renal sympathetic activity are the result of both direct actions on the kidney as well as resultant increases in angiotensin II [41–43].

Building on animal studies, a seminal study by Light in 1983 in young adult men translated this line of research into humans [44]. These investigators observed that sodium retention 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 blood pressures. 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 [45]. Reduced natriuresis with stress was noted in blacks and in those with a family history of hypertension.

These findings were replicated in studies in normotensive African-American adolescents conducted by our group [46–48]. After consuming a controlled sodium diet for 3 days prior to testing, African-American youth (ages 15–18 years) were subjected to a 5-h protocol that included 1 h of stress [47]. Thirty-two percent of the subjects demonstrated impaired pressure natriuresis with retention of sodium leading to a volume-mediated rise in BP [47]. The other subjects had a resistance-mediated rise in their pressure that resulted in natriuresis and a return of the BP to normal. The pressure response and sodium excretion during stress for the two groups are depicted in Fig. 18.3. Studies investigating stress-induced sodium retention are summarized in Table 18.1.

Factors Related to Stress-Induced Sodium Retention in Humans

It is well recognized that obesity is reaching epidemic proportions in children and adolescents. Our group has performed a series of studies examining the impact of greater adiposity on sodium retention during stress. Barbeau compared sodium handling during stress in lean versus overweight/obese black youth [49]. The overweight/obese group displayed a significantly smaller stress-related increase in sodium excretion despite a similar increase in BP. A subsequent study by Wilson was performed on a cohort of 127 youths that included both black and white subjects [50]. 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

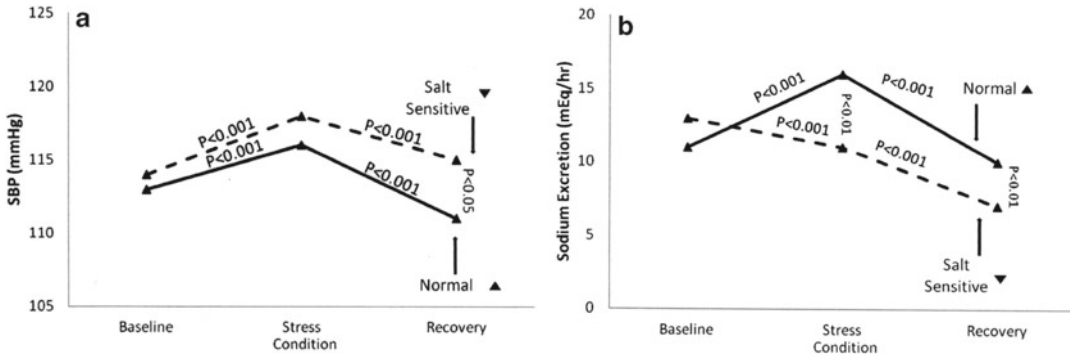

Fig. 18.3 Stress-induced changes in systolic blood pressure (*SBP*) shown in panel (**a**) and sodium excretion (*mEq/h*) shown in panel (**b**), based on direction of the stress-induced changes in sodium excretion. Data expressed as least square means. Data compared for baseline, stress condition, and recovery periods (Adapted and used with permission Harshfield GA et al. [47])

Table 18.1 Studies of impaired stress-induced sodium retention

Study	Subjects	Diet	Stressor	Duration	Results
Light et al. [44]	White males, borderline HTN or FH^+	High $Na+$/ fluid load	Competitive video games	60 min	Sodium retention in high-risk subjects
Light and Turner [45]	28 males: 14 black and 14 white	High Na^+/ fluid load	Competitive video games	60 min	Sodium retention in 43 % blacks and 14 % whites
Harshfield et. al. [46]	121 normals w/FH^+, 14–27 years old	Ad lib	Combined tasks	180 min	27 % show sodium retention
Harshfield et. al. [47]	118 black, 15–18 years old	3 days, Na^+ controlled	Competitive video games	60 min	34 % sodium retention
Harshfield et. al. [51]	292 black and white aged 15–18	3 days, Na^+ controlled	Competitive video games	60 min	Body mass index related to sodium retention in males
Barbeau et. al. [49]	84 normal black 15–18 years old	3 days Na^+ controlled	Competitive video games	60 min	Percent body fat related to sodium retention
Wilson et al. [50]	127 black and white, 15–18 years old	3 days Na^+ controlled	Competitive video games	60 min	Percent body fat and Ang II related to sodium retention
Harshfield et al. [48]	84 black and 105 white, 15–18 years old	3 days Na^+ controlled	Competitive video games	60 min	Greater sodium retention in blacks vs. whites

Adapted and used with permission from Harshfield GA et al. [33]
HTN hypertension, *Ang II* angiotensin II, *FH* family history

sodium excretion during stress. In our third study of 151 boys and 141 girls, we reported that body mass index was inversely related to sodium excretion during the stress period in boys [51]. The magnitude of the correlation became greater when only boys with a BMI>25 kg/m^2 were considered.

The propensity for salt sensitivity in African-Americans and older subjects 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 [44]. Similarly in adolescents our group found that sodium excretion in response to stress was significantly lower in blacks compared to whites (see Fig. 18.4). The stress-induced increase in urinary sodium excretion was only 2 +/− 6 mEq/h in African-American adolescents compared to 7 +/− 10 mEq/h in white adolescents [46]. With regard to the effect of age, recent data (see Fig. 18.5) from our

group has demonstrated that the magnitude of stress-induced sodium retention increases with age [unpublished data].

We have also linked sodium retention during stress to preclinical measures of target organ damage [33]. Specifically, we reported that African-American adolescents who retained sodium during stress have a 10 % greater albumin excretion rate than those that excrete sodium during stress [52].

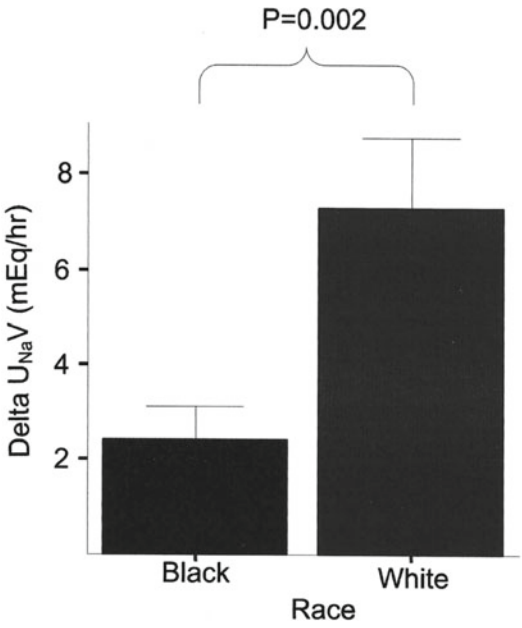

Fig. 18.4 Racial differences in sodium excretion with stress exposure. *Bars* signify change in sodium excretion (*Delta* $U_{Na}V$) expressed in mEq/hr before and after stress

Furthermore, we reported that sodium retention is associated with cardiac remodeling [46], degradation of endothelial function [53], and diastolic dysfunction [54].

Genetic Predisposition

Data on sodium sensitivity in individuals with a family history of hypertension have been conflicting. Two studies reported that stress-induced sodium retention was greater in individuals with a positive family history [44, 46], while two studies did not find differences between subjects with or without a family history of hypertension [55, 56]. We published two additional studies supporting a genetic contribution to stress-induced sodium retention. A study in twins from our group [33] reported significant heritability for sodium excretion during stress, which was greater in blacks (58 %) than in whites (42 %). 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. A second genetic study by our group identified the potential significance of the G protein-coupled receptor kinase 4 (GRK4) in sodium handling and hypertension [57]. We reported that the 65-L allele of the GRK4

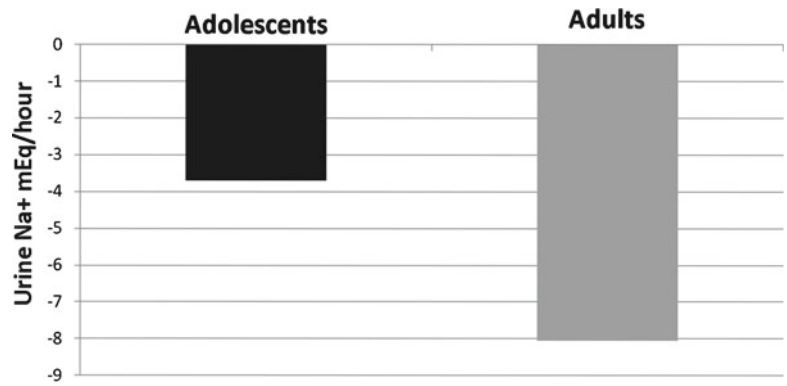

Fig. 18.5 Differences in stress-induced sodium retention in adults compared to adolescents. Urine sodium excretion during stress was compared to baseline to determine amount of retention, expressed as mEq/h

Table 18.2 Mechanisms related to impaired stress-induced sodium retention

Fauvel et al. [59]	10 HTN on ACE inhibitor 10 on placebo	Ad lib	Mental stress	60 min	ACE-improved sodium retention
Rollnik et al. [60]	21 HTN, 27 normal adult white males	5 days, 10 mEq Na^+, hospitalized	Mental stress, with monetary incentive	60 min	ACE-improved sodium retention
Schneider et al. [56]	66 normals (33 FH^+), 36 mild HTN, 18–40 years old	Ad lib	Mental stress w/ feedback intensity controlled	30 min	ACE-improved sodium retention
Harshfield et al. [51]	292 black and white, 15–18 years old	3 days, Na^+ controlled	Competitive video games	60 min	Sodium retention related to Ang II in males
Wilson et al. [50]	127 black and white, 15–18 years old	3 days, Na^+ controlled	Competitive video games	60 min	Percent body fat and Ang II related to sodium retention
GE et al. [34]	31 black, 20 white 19 ± 3 years old	Ad lib	Combined tasks	180 min	Sodium retention heritable
Zhu et al. [57]	664 twins	Ad lib	Combined tasks	180 min	GRK4 gene modulates retention

Adapted and used with permission from Harshfield GA et al. [33]
ACE angiotensin-converting enzyme inhibitor, *Ang II* angiotensin II, *FH^+* family history positive for HTN, *HTN* hypertension

gene was associated with reduced sodium excretion during stress in blacks. Overall, these studies support 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.

Mechanisms Generating Stress-Induced Sodium Retention

Studies in animals have supported the importance of the renin-angiotensin-aldosterone system (RAAS) and the SNS in the genesis of impaired sodium handling during stress. Working with Dahl rats, Koepke et al. demonstrated urine Na retention when sodium loading was followed by behavioral stress [58]. 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 [35]. A role for the SNS was also supported by work in Sprague-Dawley rats subjected to air stress [41]. 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 II antagonist.

Drawing on the above animal studies, mechanistic studies in humans have focused on the role of the RAAS (as summarized in Table 18.2). Treatment for a month with an angiotensin-converting enzyme inhibitor (ACEi) improved sodium excretion in hypertensive adults as compared to those treated with placebo [59]. Activation of the SNS was suggested by an increase in urinary norepinephrine excretion after stress. Similarly, other investigators have demonstrated that treatment with an ACEi lessened sodium retention [56, 60]. In an unpublished pilot study, we found a significant improvement in Na excretion after pretreatment with an angiotensin receptor antagonist in young adult subjects previously demonstrated to retain sodium during stress.

Perspectives

Identification of salt-sensitive individuals carries important therapeutic and prognostic implications. Unfortunately definitions and methodologies utilized to characterize salt sensitivity have varied between studies making comparison of data challenging. From a practical standpoint there is no reasonable way to identify the salt-sensitive

individual with administration of a sodium load outside of a research setting. In the office setting, salt sensitivity may be implied if BP improves with salt restriction. However, this approach is complicated by confounding factors, particularly uncertainty about the reliability of adherence. Administration of a salt load by stress-induced sodium retention is an alternative tactic to conventional sodium loading. Thus far, utility has been limited to the research arena. This link between stress and sodium retention is particularly intriguing in light of recent renewed interest in the role of the renal sympathetic nerves in generating hypertension. Esler and his colleagues have conducted studies demonstrating successful and enduring treatment of refractory hypertension with renal sympathetic nerve ablation [61, 62].

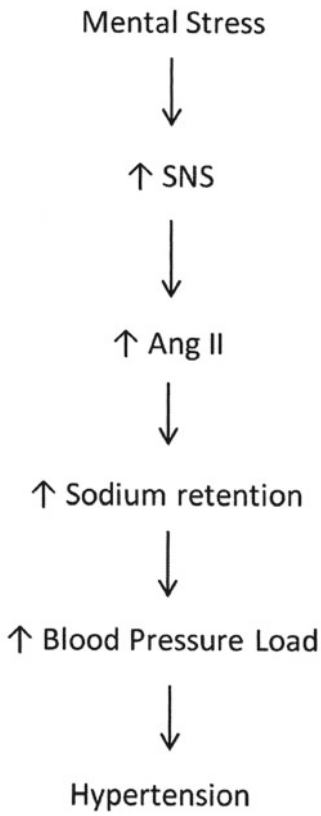

Fig. 18.6 Proposed scheme for interaction of stress, sympathetic nervous system, and renin angiotensin system in generating stress-induced sodium retention and hypertension

The 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. Our proposed model for stress-induced sodium retention addresses this interaction as shown in Fig. 18.6. Appreciation of the capacity of stress to result in sodium loading suggests new directions for treatment of salt-sensitive hypertension beyond dietary manipulations. Demonstration of impaired sodium handling during stress would identify salt-sensitive patients and enable a tailored approach to BP control. Efforts to develop an office procedure for identification of stress-induced sodium retention should be pursued.

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Hypertension in Children with the Metabolic Syndrome or Type 2 Diabetes

19

Craig E. Taplin and Joseph T. Flynn

Abstract

The childhood obesity epidemic has been accompanied by an increase in the number of young patients with complications of obesity such as the metabolic syndrome or even full-blown type 2 diabetes. Such patients 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 patients with the metabolic syndrome or type 2 diabetes, including cardiovascular effects of oral hypoglycemic agents and diabetogenic effects of certain antihypertensive medications. A comprehensive approach, including non-pharmacologic measures, hypoglycemic and antihypertensive medications, and perhaps even bariatric surgery in selected patients, is indicated in order to reduce future cardiovascular risk.

Keywords

Insulin resistance • Metabolic syndrome • Type 1 diabetes • Type 2 diabetes • Hypertension

Introduction

Of the many consequences of childhood obesity, the early development of type 2 diabetes (T2DM) is perhaps the most worrisome, given the long-term cardiovascular and renal sequelae of this condition. The metabolic syndrome (MS), a cluster of risk factors for cardiovascular disease and T2DM with 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

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children with T2DM or the MS, with a significant focus on treatment considerations, particularly as they pertain to use of hypoglycemic and antihypertensive medications.

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 the childhood and adolescent years. Therefore, the definition of HTN in the young is statistical, derived from analysis of a large database of blood pressure (BP) readings obtained in healthy children and adolescents by screening studies such as the National Health and Nutrition Examination Survey (NHANES). Normal BP in children and adolescents is defined as systolic and diastolic BP readings below the 90th percentile for age, gender, and height, while HTN is defined as systolic or diastolic BPs persistently greater than the 95th percentile [1]. There are published tables that list the normative BP values for adolescents ≤17 years of age; these are available elsewhere in this text. For adolescents ≥18 years of age, the adult BP classification scheme issued by the Joint National Commission [2] should be used. A comparison of the pediatric and adult BP classification schemes is presented in Table 19.1.

Common to both the pediatric and adult BP classification schemes is the concept of "prehypertension." This term refers to BP levels that would previously have been classified as "high normal" in older pediatric practice guidelines. While the term "prehypertension" has proven to be controversial, the concept is intended to alert patients and physicians alike that prehypertension indicates the potential for later development of HTN and, thus, a need to make lifestyle changes that might prevent this from occurring. This concept is particularly important for obese children and adolescents. In children <12 years of age, prehypertension refers to BP levels ≥90th percentile and <95th percentile; in both adolescents and adults, a BP value of >120/80 designates prehypertension.

Hypertension in the Metabolic Syndrome

The metabolic syndrome (MS) is a constellation of metabolic risk factors for developing atherosclerotic cardiovascular disease and diabetes mellitus and includes central obesity, dyslipidemia, abnormal glucose metabolism, and elevated BP. The prevalence of the metabolic syndrome in adults has been reported overall in North America as 21.8 % and increases with increasing age – 6.7 % for those 20–29 years old, 43.5 % for 60–69 years old, and 42 % for ≥70 years old [3]. Given the major increase in the prevalence of adult obesity in both the United States [4] and worldwide [5], the number of persons likely to be affected by the MS is staggering.

While it is clear that components of the MS also can be identified in children and adolescents, a consensus definition for the MS has been difficult to reach 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

Table 19.1 Classification of hypertension in children, adolescents, and adults

Blood pressure classification	Children and adolescents ≤17 years of age	Older adolescents (≥18 years of age) and adults
Normal	SBP and DBP <90th percentile	SBP <120 mmHg and DBP <80 mmHg
Prehypertension	SBP or DBP 90–95th percentile; or if BP is >120/80 even if <90th percentile	SBP 120–139 mmHg or DBP 80–89 mmHg
Stage 1 hypertension	SBP or DBP ≥95–99th percentile plus 5 mmHg	SBP 140–159 mmHg or DBP 90–99 mmHg
Stage 2 hypertension	>99th percentile plus 5 mmHg	SBP ≥160 mmHg or DBP ≥100 mmHg

Adapted from Refs. [1] and [2]
DBP diastolic blood pressure, *SBP* systolic blood pressure

Table 19.2 Proposed IDF definition of MS in children and adolescents

Ages 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
Ages 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

IDF International Diabetes Federation, *MS* metabolic syndrome

of the following constitute the MS: serum triglycerides (TG) >95th percentile, HDL cholesterol <5th percentile, systolic or diastolic blood pressure (BP) >95th percentile, and impaired glucose tolerance [6]. Using these modified criteria, Weiss et al. [6] found that 39 % of those who were moderately obese and 50 % of those who were severely obese had the MS and the prevalence increased with increasing degrees of insulin resistance when adjusting for race and degree of obesity. Using more stringent criteria, Cook et al. reported that the prevalence of MS in the NHANES III cohort was 29 % in obese subjects (BMI ≥ 95th percentile), 6.8 % in overweight subjects (BMI 85th–95th percentiles), and 0.1 % in normal weight subjects (BMI < 85th percentile)[7]. Importantly, the criteria utilized by Cook et al. to define the MS 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 MS in childhood that utilizes age-based criteria (Table 19.2) [8, 9]. Obesity is a central, essential component of their definition, with other comorbidities such as HTN. Waist circumference has been shown to be an independent predictor of insulin resistance, lipid levels, and blood pressure [10]. It is important to note that the IDF chose to compensate for variation in child development and ethnicity, age-related changes in waist circumference, and other factors. They chose not to define the specifics of the MS in children less than 10 years of age beyond obesity, suggesting that the diagnosis of MS not specifically be made. In the 10–16-year-old group, an absolute BP level was chosen, reflective of the adult MS criteria with the same cutoff points used for systolic and diastolic hypertension, rather than a BP percentile to denote elevated BP. This definition of the pediatric MS will require validation in large-scale studies [11] and should best be considered a starting point that may be changed as further data and information emerge. Recent data have suggested that further development of the MS criteria is indicated for the prepubertal age range; for example, in one recent study from Europe, features including dyslipidemia and hypertension were similarly prevalent in prepubertal as compared to pubertal and postpubertal obese children [11, 12].

Further challenges exist concerning the stability of the MS as a diagnosis in children, likely related to the dynamic state of physiological changes during puberty. This is particularly pertinent given 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 MS, as defined by various groups, including the IDF and AHA, was found to be an unstable diagnosis in approximately half of adolescents from a prospective cohort of 1,098 children with MS at baseline losing this diagnostic label on follow-up over 3 years [13]. Of course, it was also true that new diagnoses of MS in other subjects were made over the same follow-up period; capturing stability of the MS in adolescents is, thus, difficult. Ultimately, whether the use of the MS 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 as a pattern of increased cardiovascular risk seen broadly across the obese population. As a framework for the development

of an intervention plan for the individual patient, it has clinical utility.

Given that elevated BP is one of the criteria for diagnosis of the MS, it follows that the majority of persons with the MS exhibit some degree of BP elevation. Data show that HTN is strongly associated with fasting hyperinsulinemia [14] and with the cluster of dyslipidemia, insulin resistance, and obesity in children aged 11–15 years [15]. However, the association between HTN and individual components of the MS in children may be less strong. Longitudinal studies do show, though, that elevated systolic BP in childhood strongly predicts the development of adult MS [16]. The MS has been identified as a strong independent predictor of cardiovascular events in hypertensive persons, amplifying the cardiovascular risk associated with HTN [17]. The process of atherosclerosis starts at an early age and is already linked to obesity and other components of the MS in childhood [18]. Accurate identification and appropriate treatment of children and adolescents with the MS is thus critical for prevention of future cardiovascular disease.

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 prevalent adults with T2DM have coexisting hypertension and that the frequency of hypertension in this group has been increasing over the past decade [19]. Indeed, a significant proportion of adults with newly diagnosed T2DM are already hypertensive at the time of diagnosis [20]. Hypertension in adult T2DM is often poorly controlled, with only about 30 % of patients achieving the recommended target BP of <130/80 [19]. Consequently, adults with T2DM have a high rate of stroke and other severe cardiovascular disease manifestations, and premature death from cardiovascular causes is common [21].

Until recently, given that T2DM in children was rare, data were scarce on the prevalence of hypertension 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 in some ethnicities and age groups are now as likely to be T2DM as they are T1DM [22, 23], better data are emerging. In a 2006 analysis of data from the SEARCH for diabetes in youth study in the United States, among approximately 2,100 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 subjects with T2DM in the study sample [24]. 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 [25]. Disturbingly, only one-third of patients and their families were aware that they were hypertensive. 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[26] 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 – complication rates much higher than seen in children with T1DM, despite a much shorter duration of disease. Similar rates of hypertension 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 [27].

Finally, and most recently, data have emerged from the largest study of youth with T2DM to date, a randomized multicenter clinical trial called Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) [28]. This study was set up to examine the effects on glycemic control of metformin alone, metformin combined with a lifestyle intervention program, and metformin combined with rosiglitazone. Of 704 youth with T2DM with a mean duration of diabetes of less than 8 months, 26.3 % had a BP ≥90th percentile and 13.6 % had a BP ≥95th percentile.

Table 19.3 Prevalence of HTN[a] 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

Adapted from Ref. [29]
[a]Defined as BP ≥ 95th percentile, SBP ≥ 130 mmHg, or DBP ≥ 80 mmHg

No differences were seen in these rates by ethnicity; however, boys with T2DM had higher rates of hypertension than girls. In 2012, results became available after the minimum 2-year treatment period had concluded for all participants [29]. Using BP ≥95th percentile as the cutoff, a further 22 % of the study patients developed hypertension over the study period, and by the end of the 2-year follow-up period, more than 1/3 of participants in all treatment groups were hypertensive. No significant difference was found in the rates of hypertension appearance in any of the three study treatment groups (Table 19.3).

These aforementioned studies primarily use BPs obtained in clinic rather than ambulatory measures of HTN. However, in a study of obese minority adolescents with and without T2DM that incorporated ambulatory blood pressure monitoring (ABPM) [30], we found ambulatory hypertension 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 [31] 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. Alarmingly, 40 % of the adolescents in this study had microalbuminuria [30], suggesting that as in adults and as mentioned above, consistent with nonambulatory BP results, there is early development of cardiovascular disease in pediatric patients with T2DM.

With the increasing prevalence of T2DM in children and adolescents, particularly among specific minority groups [32, 33], large-scale studies can likely now be conducted to assess the importance of hypertension as a risk factor in adolescents with T2DM prospectively. The TODAY study is 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 [29]. 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 ambulatory BP monitoring and consensus definitions of hypertension into such studies will be needed to produce the most accurate assessment of early cardiovascular disease in T2DM.

In summary, emerging data suggest that the prevalence of HTN and other complications of diabetes are becoming more common and appear earlier in the course of T2DM as compared to T1DM. As high albumin excretion rates are seen in the MS in children, it seems likely that subclinical renal damage may occur before overt T2DM appears. Given the typically lower reported rates of hypertension in childhood T1DM, providers will need specific education about the importance of BP control and the risk of nephropathy in childhood T2DM.

Pathophysiology

A detailed discussion of the mechanisms underlying the development of hypertension in patients with the MS or T2DM is beyond the scope of this chapter, but a few key points deserve emphasis. Since there is considerable overlap with obesity-related hypertension, the interested reader should see Chap. 17, "Childhood Obesity and Blood Pressure." Additionally, reading discussions of the pathophysiology of obesity-related hypertension in adults [21, 34–36] would also be pertinent to pediatric patients with either the MS or T2DM.

Insulin resistance is clearly the major pathophysiological mechanism involved in the development of hypertension in both the MS and T2DM. Landsberg wrote, "…insulin resistance in the obese is a mechanism evolved for limiting further weight gain. Like any compensatory mechanism, however, there is a price to pay. In this situation, that price is the hyperinsulinemia and sympathetic activation which, via effects on the blood vessels, the heart and the kidneys, exerts a pro-hypertensive effect that, in susceptible individuals, causes hypertension" [37]. There are several lines of evidence linking hyperinsulinemia with increased sympathetic nervous system (SNS) activation and hypertension, including the finding of elevated levels of plasma catecholamines, and abrogation of hypertension after adrenergic blockade [38, 39]. While there are likely multiple mechanisms involved in activation of the SNS in the MS and T2DM [40], hyperinsulinemia is one of the most important.

There are many other mechanisms by which hyperinsulinemia may contribute to the development of hypertension. First and foremost, among these is altered renal handling of sodium, which leads to hypertension through an expansion of plasma volume. Insulin increases renal sodium reabsorption, possibly in the distal nephron, although this is not completely certain [41]. It is likely that increased renal sympathetic nerve activity is responsible, at least in part, for this effect [42]. Elevated circulating levels of aldosterone, which have been demonstrated in salt-sensitive obese adolescents, may also be involved [43]. Importantly, these effects of hyperinsulinemia on renal sodium handling can be reversed with weight loss [43].

Another mechanism by which hyperinsulinemia may elevate blood pressure is through effects on vascular structure and function. Although insulin when infused directly into local vascular beds acts as a vasodilator [44], in hypertensive subjects this effect is probably offset by vasoconstriction, mediated by increased sympathetic nervous activity [44, 45]. In addition, impaired vasodilation in response to insulin infusion has been demonstrated in obese adults [46]. Alternatively, insulin may act to stimulate vascular smooth muscle proliferation in resistance vessels via activation of the local renin-angiotensin-aldosterone (RAAS) [47], thereby leading to increased peripheral vascular resistance due to vascular medial hypertrophy. In this way, hyperinsulinemia would lead to hypertension by increasing systemic vascular resistance. This mechanism is supported by recent studies demonstrating altered vascular structure and function in obese youth with and without T2DM [48].

New data have also emerged on activation of the RAAS in obesity-related hypertension. Many components of the RAAS have been shown to be increased in obesity hypertension in adults [34], but the data in children have not been consistent. We demonstrated that in obese adolescents with or without T2DM, plasma renin activity (PRA) was positively correlated with BMI, but negatively correlated with 24-h ambulatory BP [49]. These results contrast with our prior work, which demonstrated a positive correlation between PRA and ambulatory BP [50]. Nevertheless, activation of the RAAS is likely present in many, if not all, patients with obesity-related hypertension and, as will be discussed later, may be targeted as one component of treatment of these patients.

Therapy

Since elevated BP is one of the defining criteria of the MS, 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 MS or T2DM. Given the common pathophysiology of hypertension in both the MS and T2DM, treatment of both conditions will be discussed collectively in the remaining sections of this chapter.

Role of Non-pharmacologic Therapy

(Also see Chap. 35, "Nonpharmacologic Treatment of Pediatric Hypertension.")

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 [1]. Studies in obese adolescents have demonstrated that weight loss not only decreases BP but, importantly for those with the MS or T2DM, also improves other cardiovascular risk factors such as dyslipidemia and insulin resistance [51–53]. 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. 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 [54]. However, identifying a medical complication of obesity such as the MS or T2DM may potentially provide the necessary motivation for patients and families to make the appropriate lifestyle changes.

Similarly, exercise training over 3–6 months has been shown to result in a reduction of 6–12 mmHg for systolic BP and 3–5 mmHg for diastolic BP [55]. However, cessation of regular exercise is generally promptly followed by a rise in BP to pre-exercise 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 [56]. 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 [57].

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 [58]. The combination of dietary changes and exercise training may also improve vascular function in addition to reducing BP [59].

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 [60]. Many authors have noted that the typical dietary sodium intake of children and adolescents, at least in the United States, far exceeds 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 [43, 60]. Thus, dietary sodium restriction may have a role in treatment of children and adolescents with the MS or T2DM, a substantial proportion of whom are likely to be salt sensitive.

Both potassium and calcium have been shown to have antihypertensive effects in hypertensive children and adolescents. A recent 2-year trial of potassium and calcium supplementation in hypertensive, salt-sensitive Chinese children demonstrated that this combination significantly reduced systolic BP [61]. 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 Stop Hypertension (DASH) diet, which has been shown to have an antihypertensive effect in adults with HTN, even in those receiving antihypertensive medication [62, 63]. 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 [64]. 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 MS or T2DM.

Cardiovascular Effects of Oral Antidiabetic Agents

It has become apparent over recent years that many of the agents used to improve insulin sensitivity in persons with the MS or T2DM also have important 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 [65, 66]. Studies in rats with streptozotocin-induced diabetes have demonstrated that metformin reduces BP and restores aortic endothelial function [67]. Human studies, however, have not uniformly demonstrated a significant effect of metformin on BP. For example, metformin had no effect on BP in an obese adult cohort in China without T2DM, though it did improve BMI [68]. Metformin has also been associated with weight loss in adolescents when accompanied by adherence to a lifestyle intervention [69].

Manzella et al. randomized 128 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 [70]. 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 [71]. 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 [72]. Clearly, metformin alone will be insufficient treatment for hypertension in the MS or T2DM, but it may have some beneficial cardiovascular effects. Data from the TODAY study, referenced earlier, indicate that approximately 1/3 of patients were hypertensive by the end of the trial, despite all participants being treated with metformin [29].

Rosiglitazone, a thiazolidinedione, binds to the peroxisome proliferators-activated receptor-gamma (PPAR-γ), a transcription factor that regulates the expression of genes involved in glucose production, transport, and utilization in the liver, adipose tissue, and muscle [66]. Rosiglitazone has been shown to improve vascular function and ameliorate BP in hypertensive transgenic mice [73]. Negro et al. compared the effects of rosiglitazone and metformin vs. metformin alone on BP and metabolic parameters of diabetic patients [74]. 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 [75]. Rosiglitazone has also been studied in combination with metformin with or without the addition of glimeperide, a second-generation sulfonylurea, in hypertensive type 2 diabetic patients [76] that 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. Subjects 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 [77].

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 does not confer a greater benefit with regard to HTN risk, when compared with metformin alone [29]. These minimal beneficial effects on cardiovascular risk may not outweigh the known adverse effect profile of this class of agents.

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 IV 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 [78]. One study of exenatide, a GLP-1 analogue, in adults with T2DM showed beneficial effects on systolic BP when compared with insulin or placebo [79], but these results may be confounded by weight loss, a known, likely beneficial, side effect of incretin-based therapies. The effects of inhibition of dipeptidyl peptidase IV (DPPIV), the enzyme responsible for the rapid degradation of GLP-1, on BP are even less clear. While early trials using DPPIV inhibitors in adults with the MS were not designed to examine the effect on BP [80], their effects on HTN may be dynamic and depend on interaction with the RAAS [81]. The relevance of DPPIV inhibitors to pediatric hypertension 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 [82]. 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 [83]. Insulin resistance improved in the acarbose group; however, BP declined equally in the two groups.

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 MS 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 MS 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 MS or T2DM adds impetus for starting drug therapy early in young patients with these diagnoses.

As recommended by the National High Blood Pressure Education Program [1], definite indications for initiating pharmacologic therapy in a child or adolescent include the following:

- Stage 2 hypertension (see Table 19.1)
- Symptomatic hypertension
- Secondary hypertension
- Hypertensive target-organ damage
- Diabetes (types 1 and 2)
- Persistent hypertension despite non-pharmacologic measures

Thus far, although it might seem reasonable to add the presumptive diagnosis of the MS 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 MS in pediatrics discussed earlier. At the very least, children and adolescents with the MS and BP above the prehypertensive range who do not adhere to or respond to a reasonable (6–12-month) trial of non-pharmacologic measures should probably be prescribed antihypertensive medications, given the high risk of progression of the MS 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 hypertension is covered in detail in Chap. 36, "Pharmacologic Treatment of Pediatric Hypertension," so the following discussion is limited to specific aspects pertinent to the MS and T2DM. One of the key general principles of treatment of hypertension 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 [2], which highlighted a list of "compelling indications" that, based upon the results of large-scale clinical trials, favored the use of specific drug classes. Included in the JNC-7 list of compelling indications is diabetes, and drug classes listed as indicated included ACE inhibitors, angiotensin receptor antagonists, diuretics, beta-blockers, and calcium channel blockers. Choosing between these in a patient with T2DM may depend upon the presence or absence of microalbuminuria, in which case an agent affecting the renin-angiotensin-aldosterone (RAAS) would be favored [84]. Unfortunately, a similar evidence base is lacking for pediatric patients, as studies including pediatric and adolescent patients with these co-morbid 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 MS 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 [85, 86]. Alpha-blockers lower triglyceride and free fatty acid levels and have no effect on total, high-density, or low-density cholesterol [86], important considerations given the common finding of dyslipidemia in the MS 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 MS [87].

Calcium channel blockers have also been demonstrated to have beneficial effects on insulin sensitivity in patients with essential HTN [88, 89],

so, by extension, would be appropriate for use in persons with the MS. 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 MS [90, 91]. Additionally, since the RAAS is likely activated in patients with obesity-related hypertension (which would include the MS and T2DM) [21, 34–36], there is a specific pathophysiological basis for using these agents. Some of the newer ARBs appear to activate PPAR-γ, producing the beneficial effects of the thiazolidinediones without the weight gain and other potential adverse effects associated with those agents [92]. Therefore, many authors recommend ACE inhibitors and ARBs as the first-line agents for treatment of HTN in patients with the MS [93].

In contrast, diuretics and beta-adrenergic blockers are usually thought to have "diabetogenic" potential [94] and should probably be avoided as initial agents in treating HTN in patients with coexisting MS [95]. This position is supported by reanalysis of data from the ALLHAT study [96], which demonstrated a greater incidence of new-onset diabetes in the group treated with chlorthalidone as compared to those treated with amlodipine or lisinopril [97]. 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 [98].

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 [93]. 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 β-1 selective adrenergic blocker nebivolol [99]. 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 β-1 selective adrenergic blocker metoprolol [100]. Thus, it may be reasonable to include selected non-thiazide diuretics and β-1 selective adrenergic blockers as part of the treatment regimen in patients with diabetes.

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 [101]. 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 end points 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) is recommended than in those with uncomplicated HTN (140/90) [2], a recommendation based on the results of large-scale clinical trials involving thousands of patients. Lacking large-scale trials in pediatric hypertension, the National High Blood Pressure Education Program (NHBPEP) has developed a similar recommendation for children, based upon expert opinion – 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 [1]. Recent pediatric guidelines issued by the European Society of Hypertension suggest lower BP goals than those in the Fourth Report [1] and also recommend frequent use of ambulatory BP monitoring to guide therapy [102].

There are no data to guide the treatment of patients with MS but not 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 MS. In older hypertensive adolescents aged ≥18 years with the MS or T2DM, JNC-7 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 [103]. It may be more effective in youth than in adults in reversing the metabolic complications of obesity, and these may precede significant weight loss [104]. Further data are required, but in an uncontrolled study, HTN resolved in 14 severely obese adolescents who underwent bariatric surgery [105]. However, there are many questions about the role of bariatric surgery in the management of obesity in the young [106] 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 MS or T2DM.

Summary

The high prevalence of obesity in children and adolescents is now known to be accompanied by numerous complications, including the MS and T2DM. Although there is still some uncertainty regarding the optimal definition of the MS in the young, its core components, most notably HTN, are readily detectable in MS and T2DM. HTN in obese children with or without T2DM is characterized by abnormalities on ambulatory BP monitoring and may be diagnosed earlier using this technique. Therapy 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.

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Primary Hypertension in Children

20

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Abstract

Primary hypertension in children is not as common as in adults; recent studies suggest a prevalence of 3–4 % in the pediatric population. However, more recent reports have highlighted an increasing prevalence of HTN and prehypertension, likely due to childhood obesity. Given the global burden of hypertension, identification and management of primary HTN is beneficial to the individual child and has important implications for society as well, particularly since tracking studies have established that adult primary HTN has its antecedents during childhood. Studies are limited on the pathophysiology of primary HTN in children; 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 HTN in children as well. Primary HTN in young children is a diagnosis of exclusion, and selective workup is needed to rule out any underlying secondary causes; however, in adolescents, primary hypertension is much more common than secondary hypertension. 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

Introduction

The diagnosis of hypertension accounts for 58–65 million hypertensive adults in the United States alone and is also the most common diagnosis for outpatient physician visits and prescription drugs [1, 2]. Primary HTN is believed to have its antecedents during childhood. Studies

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have shown that the relationship between arterial pressure and mortality is quantitative; the higher the pressure, the worse the prognosis [3]. Therefore, it is important that those providing care to children approach the issue of HTN both as a societal challenge and as a disease affecting discrete individuals.

Prevalence

Primary hypertension is prevalent in 29–31 % of the adult US population and nearly 44 % of the adults in Europe [4]. It is difficult to estimate the worldwide prevalence of pediatric HTN due to regional differences in definition and normative values used to diagnose hypertension. In the United States, recent screening studies and survey data have given an estimated prevalence of 3–4 % [5–8] in the pediatric population.

More recent reports have highlighted the effects of childhood obesity on the prevalence of HTN and prehypertension in children and adolescents [8, 9]. 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 HTN [9, 10].

Incidence

Data on the incidence of HTN 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 1,000 adolescents [11] 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 [12], these findings could potentially translate into nearly half a million hypertensive adolescents after 5 years.

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 HTN, increased body weight, or increased left ventricular mass [13–16]. This is indicative of the interaction between the genetic and environmental factors influencing BP. The Muscatine Study, for example, has demonstrated that primary HTN in young adults has much of its origin during the childhood years [17]. Although the strength of the tracking phenomenon has been questioned [18], 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 [19] (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 girls < 92/62 at 5 years, boys < 104/64 girls < 102/64 at 14 years, boys < 115/67 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 the current Fourth Task Force Report recommendations [20]. 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 [19].

Definitions and Techniques

Criteria for making a diagnosis of primary HTN are summarized in Table 20.1. As per the current recommendations, BP readings of more than 95th percentile for sex, age, and height on three separate occasions are required for diagnosing HTN. The most widely used nomograms for BP in children are those provided in the Fourth Task Force Report on Blood Pressure in Children and Adolescents [20].

According to the recommendations of the Fourth Task Force Report, pediatric HTN is now categorized into pre-HTN (SBP or DBP between the 90th and 95th percentile or greater than 120/80 in adolescents), stage 1 HTN (SBP or DBP ≥95th percentile up to the 99th percentile plus 5 mmHg), and stage 2 HTN (SBP or DBP >99th percentile plus 5 mmHg). Children and adolescents with primary hypertension may present with either stage 1 or stage 2 HTN [10, 21]

Primary HTN in children is often associated with a family history of HTN or other cardiovascular disease. Other comorbid conditions associated with primary HTN in children, which increase the risk for cardiovascular disease, include abnormal lipid profile, glucose intolerance, and sleep abnormalities.

Some researchers have questioned the validity of the current definition of HTN in children [4]. HTN is defined by a statistical cut point in the continuum of BP nomograms derived from different epidemiologic studies using a rigorous study protocol [5, 20, 22]. The definition of HTN is concurrent with an increased risk of recognizable morbidity and mortality that becomes increasingly prevalent as BP increases. A pragmatic definition of HTN 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. As of this writing, there are no data that adequately define this in children. This is in contrast to adults, where in outcomes data in terms of increased cardiovascular morbidity or mortality is used to define normal versus elevated BP.

As reviewed by Collins et al. [4] the recommendation of using three BP readings to diagnose HTN may in fact underdiagnose HTN in children. Currently there is no data to demonstrate that 2 BP readings are better or inferior in identifying hypertensive children. The same review [4] also highlights the limitations of using the statistical definition of HTN for minority ethnic groups, such as African Americans, who may have a higher prevalence of HTN and associated end-organ damage. The use of Gaussian distribution curves would diagnose HTN at much higher levels in these groups and possibly delay indicated interventions [4]. However as reviewed by Flynn et al. [23] the fundamental question that remains unanswered is what BP is nonphysiological 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 consensus organizations [20, 22]. 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 [20]. Many of these issues are discussed in detail in Chap. 9.

Table 20.1 Criteria to use in diagnosing primary HTN in children

Primary criteria
➢ An average of 2–3 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 HTN
Supportive criteria
➢ Stage 1 HTN on presentation
➢ Children obese on presentation (BMI > 95th percentile)
➢ Family history of HTN
➢ Idiopathic HTN associated with high, normal, or low PRA
➢ Abnormal response to mental stress
➢ Evidence of end-organ effect; funduscopic changes, cardiac enlargement by electrocardiogram and/or echocardiogram (suggestive of long-standing HTN)

Ambulatory blood pressure monitoring (ABPM) has been used increasingly to diagnose HTN, define diurnal BP variability in normal and hypertensive populations (including children) [24], and to evaluate therapy. ABPM overcomes many of the measurement issues associated with office BP measurement, is essential for diagnosing white-coat HTN, and may sometimes help to distinguish primary versus secondary HTN in children [25]. ABPM is discussed in depth in Chap. 11.

BP Homeostasis and Pathophysiology of Hypertension

The wide variety of factors involved in regulating blood pressure are discussed in detail in an earlier section of this text and have been reviewed in detail elsewhere [26, 27]. A brief overview of the factors determining BP is presented here, however, as it is necessary to understand the steps involved in the generation and persistence of primary HTN (Table 20.2). Due to paucity of pediatric studies, most of the discussions below are based on adults and animal studies. However evidence from tracking studies suggests that the proposed multifactorial and complex genetic, environmental, and biological interactions involved in development of hypertension in adults would provide a basis to understand HTN in children as well.

HTN occurs when the sum of cardiac output (CO) and total peripheral resistance (TPR) increases. The factors involved in increasing BP during the generation and maintenance of primary HTN are often different. In one form, the increase in 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 [28, 29]. Fixed persistent primary HTN is characterized by an increase in TPR and a return to a normal CO. In the second form, early HTN 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 HTN [30]. The observed changes, from that of an increased to normal CO, and an increased TPR over time enable a constant blood flow to organs in experimental animals and humans. The presence of functional versus irreversible structural changes explains response to therapy and the potential reversibility of the hypertensive process aggravated by obesity, stress, and/or excessive salt intake.

Table 20.2 The basic blood pressure formula and its physiologic transformation to HTN

1. Pressure equals flow times resistance
2. BP = volume times resistance
3. BP = CO times total peripheral resistance
4. BP = flow (preload + contractility) x resistance (arteriolar functional contraction + vessel anatomical changes), for example, BP = flow x resistance
5. HTN = a net increase in CO and/or increased peripheral resistance

Kidneys maintain intravascular volume by regulating sodium and water excretion and subsequently are the primary influence on the long-term control of BP. The two main renal mechanisms involved 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 salt and water in response to elevated arterial pressure to maintain BP by regulating body volume. Despite the wide variations in sodium intake, the kidneys through a tightly regulated balance of glomerular filtration and tubular secretion/absorption are able to maintain a constant BP. RAAS influences both elements of the BP formula. Renin is secreted by the juxtaglomerular cells of the kidney in response to physiological and nonphysiological reduction in BP, renal blood flow, and sodium chloride load at macula densa. ANG II is the effector arm of the RAAS and it increases vascular contractility and thereby peripheral resistance by binding to AT1 receptors present on the vascular smooth muscle. ANG II

binding within the adrenal gland leads to increased aldosterone production, sodium retention by the kidney, and volume expansion. The AT2 receptor, which is not involved in the vascular/smooth muscle contraction, is known to play a role in cell differentiation and hypertrophy. The central role of the RAAS in hypertension has recently been reviewed elsewhere [31].

Genetic renal defects linked with *abnormal sodium homeostasis* in primary HTN include increased efferent arteriolar tone leading to increased sodium reabsorption, congenital reduction in the number of nephrons and filtering surface [32], nephron heterogeneity [33], and non-modulation that involves abnormal adrenal and renal responses to angiotensin (ANG) II infusions [34]. Single-gene disorders that affect renal sodium handling are discussed in more detail in Chap. 6.

Recent research in animal models has highlighted the role of medullary circulation in pressure natriuresis and pathogenesis of hypertension [35]. Increased medullary blood flow is associated with increase in 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 HTN [35].

Nephron heterogeneity [33] 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 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 [36] 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 without in the vessel-media cross section. 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 towards the vessel lumen with apoptosis in the periphery and altered smooth muscle motility of the vessel wall [36, 37]. 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 other antihypertensives [27, 36, 37].

Laragh et al. have proposed that patients with primary HTN can be divided into three groups: normo-, hyper-, and hyporeninemic based on *renin profiling*, for example, the comparison of plasma renin activity (PRA) to sodium excretion [27, 38]. This group concluded that high-renin primary HTN patients are at greater risk for vaso-occlusive events such as stroke, infarction, and renal failure, while those with low-renin primary HTN are volume overexpanded and less likely to experience the aforementioned end-organ damage. Moreover, they suggest that drug therapy should be targeted at the underlying primary pathophysiology, and renin inhibitors and diuretics be, respectively, used to treat patients with high- and low-renin primary HTN. Limited studies in children have included renin profiling and the incidence of low-renin HTN is estimated at 19 % [39]. There is currently no long-term data on the outcome of hypertensive children, who were renin profiled at diagnosis. Studies have also shown that PRA is higher in those with high uric acid levels and inversely related to fractional excretion of uric acid in hypertensive patients [40]. This suggests the presence of altered glomerulotubular balance in hypertensive patients. Feig et al. have recently reported that hyperuricemia (uric acid >5.5 mg/dl) is more commonly associated with primary HTN compared to secondary or white-coat HTN [41].

Sympathetic nervous system (SNS) activity can function as an initiator and as a secondary contributing factor for elevated BP. Stress and/or a primary catecholamine regulation defect in the brain may directly cause vascular vasoconstriction. SNS stimuli from the vasomotor center activate efferent pathways causing norepinephrine

release at peripheral nerve endings, which in turn stimulate adrenergic receptors. Circulating epinephrine derived from the adrenal medulla can stimulate norepinephrine release through stimulation of presynaptic β-2 receptors. Excessive circulating catecholamines increase the BP response to a sodium load. Baroreceptor reflex arc dysfunction occurs in some patients with primary HTN. Usually, elevated BP leads to reflex lowering of the BP by reducing sympathetic outflow from vasomotor centers and increasing vagal tone. The responsiveness of this system resets itself to a higher level with BP elevations and plays a role in the persistence of HTN. Impaired circulatory homeostasis and 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. Although *dopamine* is a modulator of systemic BP, with additional actions on fluid and sodium intake, no mutations have linked patients' primary HTN or genetic HTN in animal models to the D1 receptor.

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. [42], 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 intrauterine period being a critical period for development of primary HTN (discussed in detail in Chap. 7) [43, 44].

Barker first proposed that HTN in adult life is associated with retarded fetal growth and this relationship becomes stronger as the patient ages [43, 45]. Postulated mechanisms include insulin resistance, exposure of a malnourished fetus to maternal glucocorticoids that alter subsequent steroid sensitivity, as well as the metabolism of placenta cortisol [46], and the presence of a reduced number of glomeruli. The net result is a reduced number of glomeruli (as much as 25 % in experimental animals), a decreased glomerular surface area, and a reduction in glomerular filtration rate (GFR) per nephron [47]. The impaired nephron function eventually leads to HTN. A similar outcome has been reported with the blockage of the RAS with losartan after birth. Studies in rats have shown that young rats are at higher risk for salt-sensitive hypertension compared to older rats, hypertensive response to salt is more marked at young age, and antihypertensive therapy is effective and may have preventive effect on hypertension when started earlier. The identification of similar critical periods in humans could have significant effects on hypertension research [42].

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 20.3). Due to its central role in BP regulation, gene polymorphisms of the RAAS system have been frequently evaluated in hypertensive patient cohorts. Current evidence links genes controlling plasma angiotensinogen (AGT) with risk for HTN, while no conclusive association is reported with the ACE gene polymorphisms [48, 49]. Angiotensinogen M235T genotype has been associated with increase in angiotensinogen levels and increased risk for hypertension [49]. The theory of impaired genetic homeostasis postulates [50] 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 HTN. Synchronicity, a process by which growth spurts are associated with increases in BP, may be accelerated in genetically prone hypertensive individuals [51]. Allometric dysfunction, a process by which somatic and renal growths fail to match each other, might lead to HTN if environmental factors enable excessive non-genetically determined growth to occur [52]. 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 HTN [53]. Finally, perturbation in neural development of the sympathetic nervous system and/or cardiac β1-receptors may predispose newborns to develop a hyperkinetic circulation and, therefore, HTN [54].

Table 20.3 HTN and gene studies

Genome-wide association study (GWAS)	
Strengths – hypothesis-free studies, lead to discovery of new genes	
Weaknesses – large sample size is needed to detect meaningful association, higher study costs, need for stricter quality control, and handling of large databases	
Linkage reported in most of the chromosomes, however there is little current clinical application	
➢ WTCC [86], Saxena R [87], Levy D [88], Kato N [89], Sabatti C [90] – no significant genome-wide association	
➢ Global BPGen study [91] – 8 regions with genome-wide significance in chromosomes	
➢ CHARGE study[92] – significant genome-wide associations between 13 SNPs with SBP, 20 SNPs with DBP and 10 SNPs with HTN	
Genome search meta-analysis (GSMA) – meta-analysis of the GWAS	
➢ Levy D [82]	Global BPGen and CHARGE meta-analysis 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/HTN SNP ATP2B 12q 21–23 associated with significant association with SBP/HTN
➢ Wu X [93]	No locus achieving significant linkages; suggestive linkage at 2p14 and 3p14.1
➢ Koivukoski [94]	Significant association with DBP and HT at 2p12-q22.1, 3p14.1-q12.3
➢ Liu [95]	No genome-wide significant linkage to HTN
Candidate gene analysis	
Strengths – known pathophysiological processes associated with HTN are studied at genetic level, and animal data is available on these genes, compared to GWAS that are low cost	
Weaknesses – HTN is polygenic and individual genetic contribution to HTN phenotype may be small, cannot evaluate gene/environment interaction, and have less chance for identifying newer genetic pathways linked to HTN	
➢ G-protein system [96] – G-protein β3-subunit (GNB3) gene C825T polymorphism, G-protein receptor kinase 4 (GRK4) gene, Gαs subunit (GNAS) gene	
➢ α-Adducin gene (ADD1) gene, Gly460TRP polymorphism[97]	
➢ Polymorphisms of CYBA gene encoding p22 phos subunit of the NADPH oxidase system[98]	
➢ Renal sodium transporters[99]; SCNN1B gene encoding β-subunit of ENaC transporter β-ENaC G589s polymorphism, SLC9A3 gene encoding NHE 3 exchanger in proximal tubule	
➢ RAAS genes[100, 101]: (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 (AT1R), (4) CYP11B2 aldosterone synthase gene C344T polymorphism	
➢ Genes linked with changes in vascular tone [102]; a*drenergic receptors*; (1) α1a gene 347 Cys polymorphism, (2) α2a gene Dral polymorphism, (3) α2b gene Glu 301–303 deletion variant, (4) α2c insertion/deletion polymorphism *nitric oxide (NO)* endothelial NO synthase gene on chromosome7 G849T polymorphism	
➢ *Adenosine monophosphate deaminase (AMP)* AMP-1 (AMPD 1) gene polymorphism *endothelin* 1 gene polymorphisms and G-protein polymorphisms	
➢ Mitochondrial gene mutations[99, 103]; mitochondrial NADH dehydrogenase 3 gene A10398G mutation	
Large-scale candidate gene studies	
➢ Sober S [104], Padmanabhan S [105], Tomaszweski M [106] – no significant association with BP candidate genes	
➢ Johnson T [107] replicated SNP for angiotensin locus AGT and ATP2B1 locus of other studies and reported other novel loci	

Risk Factors Involved in Childhood Primary HTN

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 HTN is the most common cause of HTN in older children especially in the postpubertal group. The prevalence of HTN and pre-HTN is greater in boys than girls [55]. Also, in girls BP rises rapidly between 6 and 11 years as compared to 12–17 years, while the opposite is seen in boys [56]. The male preponderance of high BP persists

till 50 years of age, when BP levels in women again exceed men's [56].

Race and Ethnicity

The prevalence of primary HTN is clearly influenced by race and ethnicity [57]. Native Americans have the same or higher rate of primary HTN as Hispanics who have the same or lower BP than Caucasians. The prevalence of HTN in blacks is twice that of whites, has an earlier onset, and is associated with more end-organ damage. These differences are most likely quantitative [58] 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 [59]. Blacks have higher sleep and less dipping in their nighttime ABPM values than age-matched whites [60]. Blacks 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 [61, 62].

Genetics and Family History

Up to 40 % of HTN is attributable to genetic factors indicating increased risk for hypertension in genetically related individuals [63]. 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/HTN. 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 20.3). 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.

Obesity

Obesity, which is found in 35–50 % of hypertensive adolescents, is one of the most important factors involved in both the generation and persistence of childhood primary HTN [9]. Prevalence studies, including tracking studies of weight change and BP in young adults [64], have reported an increase in childhood obesity and HTN in obese subjects. The relationship between elevated BP and weight begins in early childhood and has been reported to occur as early as 5 years [65]. The Muscatine Study showed that changes in ponderosity over 11 years correlated directly with BP changes [17]. Obesity is associated with the "metabolic syndrome," which is characterized by insulin resistance, an atherogenic dyslipidemia, activation of the sympathetic nervous system, and an increased tendency for thrombosis (see Chap. 19). Other suggested mechanisms of obesity-related HTN include hyperinsulinemia, hyperproinsulinemia, renal sodium retention, increased sympathetic activity [29], increased plasma volume, increased levels of dehydroepiandrosterone [66], and increased CO. Increased plasma aldosterone activity in obese adolescents correlates with increases in their mean BP; the BP level falls when weight loss occurs [67]. Obesity hypertension is discussed in more detail in Chap. 17.

Salt Intake

It is estimated that since the Paleolithic period, the average sodium intake in the human diet has increased almost fivefold to approx 3,400 mg/d, a level sufficiently high enough to enable high-BP expression in salt-sensitive individuals [68]. 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 [69]. He et al. [70] 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.

Table 20.4 Role of sodium in primary HTN

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 with essential HTN, BP varies directly with changes in sodium intake
➢ Decrease in salt intake in people with borderline high BP may prevent the onset of HTN
➢ The time and quantity of sodium administration to rats genetically predisposed to HTN 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 HTN, nor does BP rise with age
➢ Primitive isolated societies increase their BP after being exposed to environments where excess sodium is ingested

Experimental studies (Table 20.4) have shown that the amount and time of introduction of sodium in the diet of newborn rats influences the onset and persistence of HTN. In human neonates, the ingestion of lower sodium (4 meq/L) containing formula after birth was associated with a 2.1-mm/Hg lower BP after 6 months [71]. Even though this difference did not persist a few years later, it is still possible that a life-long 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 Americans, 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. In hypertensive children, the issue of salt restriction has not been fully evaluated in context of their requirements for growth and development.

White-Coat HTN (WCH)

WCH or isolated office HTN is defined as office BP readings ≥95th percentile but with normal values outside the clinical setting. The estimated prevalence of WCH is around 35 % in children being evaluated for persistently elevated casual BP and 44 % in children with a family history of primary HTN [72]. The prevalence of white-coat HTN is higher when the office values reveal borderline or mild HTN and much lower with moderate or severe HTN [73]. 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 HTN [74]. Increased urinary excretion of cortisol and endothelin in adolescents with WCH identifies a group with distinct metabolic abnormalities [75]. 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 HTN (prehypertensive) [76] and one that will remain normotensive outside clinical setting.

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. [77] 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. WHO's latest guidelines recommend 60 min of at least moderate intensity physical activity in addition to activities of daily living [78]. 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, 3 times/week, and intensity sufficient to improve aerobic fitness is sufficient to decrease BP in hypertensive children [78]. Gopinath et al. [79] 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 [80]. 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 [81].

Lipids and Cigarette Smoking

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 % [82]. 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.

Harmful effects of smoke exposure, active or passive, on the cardiovascular status have been shown in adults [83]. 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. [84] have reported that environmental nicotine exposure as a consequence of parental 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.

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. Both SBP and DBP can be correlated with chronic hostility, nervousness, and the demanding perception of environment in adolescents [72]. Type A behavior is associated with increases in SBP, but not DBP [73]. Three models of psychosocial stress that might explain the genesis of primary HTN are the Defense Defeat Model, Demand Control, and Lifestyle Incongruity Index [74]. 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.

Conclusions

The increasing diagnosis of primary hypertension in children represents an important shift in our understanding of pediatric hypertension. Primary hypertension in children is a diagnosis of exclusion and children need selective evaluation for any underlying secondary cause. Elevated BP in children is associated with end-organ effects (for a detailed discussion, see Chap. 29). Studies have reported increased prevalence of left ventricular hypertrophy, vascular changes, microalbuminuria, and impaired cognitive function in children with elevated BP [4, 85]. Early identification and management of elevated BP in the pediatric population is important to decrease the risks for end-organ injury.

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Secondary Forms of Hypertension in Children and Adolescents

21

Smitha R. Vidi and Kevin E.C. Meyers

Abstract

Secondary forms of hypertension are more common in children than in adolescents. 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. Although adolescents have a higher incidence of elevated BP compared to young children, teens more often have primary rather than secondary hypertension. 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 that could help direct the most cost-effective work-up are needed and would also reduce the likelihood of missing a treatable cause of hypertension.

Keywords

Secondary • Hypertension • Renovascular • Parenchymal • Coarctation of aorta • Endocrine

Introduction

Measuring BP is now a standard part of routine health assessment in childhood. Recent reports indicate that the prevalence of hypertension in children (based on repeated measurements) is about 3.5 % [1, 2]. Although primary hypertension may occur in childhood and is quite common among hypertensive adolescents, secondary hypertension is more likely than primary hypertension in children under 12 years [3]. Secondary forms of hypertension are those with an identifiable cause for the increased blood pressure (BP). Approximately 70–85 % of all children between 0 to < 12 years of age and 10–15 % of all adolescents 12–18 years will have an identifiable secondary cause for hypertension [4].

Most causes of secondary hypertension are readily identifiable. However, the actual clinical

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conundrum is trying to identify a secondary cause for hypertension in a child or adolescent when none is obvious. The presence of four features – absence of clinical signs or symptoms, a normal serum creatinine, a positive family history, and an elevated BMI – increases the likelihood of primary hypertension [5]. In a report from the Midwest Pediatric Nephrology consortium among 246 referred patients, there was no difference in age, distribution of weight, or stage 2 hypertension in those with primary versus secondary hypertension [6]. 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 that would help direct the most cost-effective work-up and would also reduce the likelihood of missing a treatable cause of hypertension.

In the following sections, we will present an overview of the major secondary causes of hypertension in the young. Detailed discussions of many of the conditions mentioned can be found elsewhere in this book. Other specific aspects of the diagnostic evaluation of hypertensive children and adolescents are discussed in Chap. 32.

Causes of Secondary Hypertension in Children

Children and adolescents with secondary causes for hypertension can be divided into two broad categories:

- Patients with clues in the history and physical examination that help to reach a diagnosis of secondary hypertension (Tables 21.1 and 21.2)

Table 21.1 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	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; APSGN
7.	Neurological	Head injury, seizures, altered mental status, increased intracranial pressure, autonomic instability, pain related
8.	Orthopedic	Long bone fracture; traction
9.	Mediations/drugs	OTC nasal decongestants containing ephedrine/pseudoephedrine; cocaine and amphetamines; steroids and calcineurin inhibitors

Table 21.2 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; absent femoral pulses; ejection systolic murmur
3.	Renovascular	Fever, malaise, signs of claudication; absent femoral pulses; abdominal bruit; features of NF1,TS, Williams, 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 nighttime awakenings; daytime somnolence

- Patients who are asymptomatic and have a normal examination and who may or may not have a secondary cause for hypertension

Renal Parenchymal Disease

Acute Glomerulonephritis

Hypertension in children with acute glomerulonephritis (AGN) has an acute onset in a previously normotensive child. Such hypertension is usually seen in a child with macroscopic hematuria with red cell casts in the urine, oliguria, and signs of intravascular volume overload. The acute increase in BP may be secondary to water and sodium retention, activation of the renin-angiotensin-aldosterone system (RAAS), disturbance of endothelial nitric oxide balance, and/or endothelin release. This form of hypertension is easily identifiable based on the patient's history and the presence of red cell casts in the urinary sediment and evidence of acute kidney dysfunction. This type of hypertension usually resolves within a few weeks of onset and is unlikely to lead to chronic BP elevation.

Polycystic Kidney Disease

Hypertension is seen in children with both autosomal recessive polycystic kidney disease (ARPKD) and autosomal dominant polycystic kidney disease (ADPKD) and may be the initial manifestation of the condition (Fig. 21.1). Hypertension is often severe in ARPKD, especially when present in newborns and infants. Only 10–20 % of children with underlying ADPKD present with hypertension as compared to adults, the majority of whom present with hypertension prior to any loss of renal function [7]. Children with ARPKD have certain clinical features that usually help distinguish them from those with ADPKD – a neonatal history/antenatal diagnosis, enlarged kidneys, hepatosplenomegaly, cholangitis, portal hypertension and esophageal varices, progression to ESRD in childhood or adolescence, and a negative family history for PKD. Children with ADPKD may have a family history for PKD, progressive enlargement of the kidneys with macroscopic cysts in the cortex and medulla, and extrarenal cysts. A family history of cerebral aneurysms may be present, and aneurysms may be present in children with ADPKD, though most sources do not support screening young children with known ADPKD.

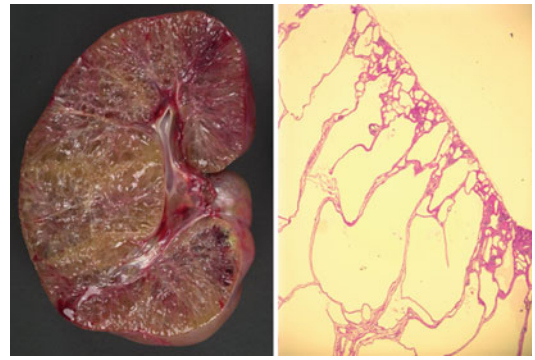

Fig. 21.1 ARPKD and hypertension. The infant had severe hypertension and pulmonary hypoplasia. The enlarged kidney of 14 cm shows dilated collecting ducts arranged in a *radial pattern*

The RAAS plays a key role in the pathogenesis of PKD-associated hypertension. In ARPKD there is intrarenal renin release with ACE gene upregulation by abnormal collecting tubule epithelia and impaired salt and water excretion [8]. In ADPKD, RAAS activation is considered to be due to local ischemia caused by enlargement of cysts. Hypertension is an early marker of disease progression in children with ADPKD. In a recent randomized study in children with ADPKD and borderline hypertension (75th to 95th percentiles), controlling blood pressure with an angiotensin-converting enzyme inhibitor stabilized kidney function and left ventricular mass when compared with untreated children [9].

Congenital Abnormalities of the Kidneys and Urinary Tract (CAKUT)

CAKUT comprises a wide range of renal system structural and functional malformations that occur at the level of the kidney (e.g., hypoplasia and dysplasia, horseshoe kidneys, renal agenesis), collecting system (e.g., hydronephrosis and megaureter, unilateral duplex ureter), bladder

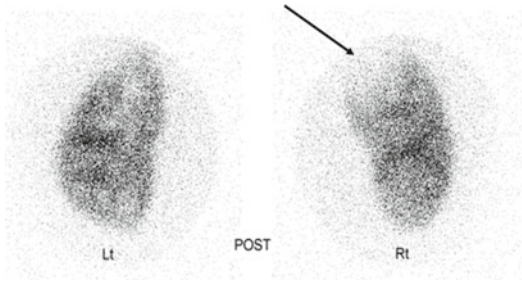

Fig. 21.2 DMSA scan with cortical scarring secondary to vesicoureteric reflux. A 5-year-old with a previous history of febrile UTI and vesicoureteric reflux. He was noted on routine examination to have stage 1 hypertension. A dimercaptosuccinic acid (DMSA) scan done as part of the work-up for hypertension shows a right upper pole scar (*arrow*). Blood pressure was controlled with a small dose of an ARB

(e.g., ureterocele and vesicoureteral reflux), or urethra (e.g., posterior urethral valves).

Many of the patients with these abnormalities have sodium and water wasting due to damaged tubules; hence, hypertension is not usually an initial manifestation of the condition. However, renal scarring after pyelonephritis (Fig. 21.2), dysplasia, and hypoplasia predispose to the development of hypertension and proteinuria as CKD progresses [10].

Chronic Kidney Disease

Many children with CKD have hypertension. Whether elevated BP is present is influenced by CKD stage/GFR as well as etiology of CKD. When hypertension is present in a child with CKD, it usually requires pharmacologic therapy for BP control. The prevalence of hypertension increases with decreasing GFR [11], and hypertension in children with CKD (as in adults) has clinically important implications for the progression of both renal and cardiovascular disease [12]. Cardiovascular complications in children with CKD include cardiac hypertrophy and carotid artery thickening, which are biomarkers for cardiomyopathy and atherosclerosis (see Chap. 29). 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 as well as assessment of cardiovascular structure and function [13]. Precise longitudinal GFR evaluation should help answer questions about the effect of BP on cardiovascular outcomes and progression of CKD in children [14]. Hypertension in CKD is discussed in more detail in Chap. 22.

Renovascular Disease

Renovascular disease as an underlying cause of hypertension occurs in about 10 % of hypertensive children and in less than 5 % of hypertensive adolescents [15]. Children and adolescents with renovascular disease usually present with stage 2 hypertension. Clues suggesting renovascular disease in children and adolescents are summarized in Table 21.2

Specific forms of renovascular hypertension that may be seen in children are discussed in detail in Chap. 24.

Vasculitis

The most common primary vasculitides that may cause hypertension in children are Takayasu's arteritis and polyarteritis nodosa (PAN). 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 and is more frequent in Japan, China, Southeast Asia, and parts of Africa. 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) [16].

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, and slowly progressive renal insufficiency. Hypertension may be related to renal artery aneurysm formation, rarely to renal artery stenosis, to renal parenchymal infarction, and to occurrence of interstitial nephritis [17].

Extrinsic Compression and Other Causes of Secondary Hypertension

Tumors may cause compression of the renal vasculature, with renin release resulting in hypertension. Renovascular hypertension and obstructive uropathy may occur after treatment of large tumors, in which radiotherapy and postoperative fibrosis may result in RAS or ureteral stricture [18] (Fig. 21.3). Renal artery stenosis also develops in 1–2 % of pediatric renal transplant recipients [19, 20].

Renal venous thrombosis (RVT) and renal artery thrombosis (RAT) can result in hypertension. Renal venous thrombosis 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 renal venous thrombosis often presents with the classic triad of hematuria, a palpable flank mass, and thrombocytopenia. Hypertension develops in about 19 % and 22 % of those with unilateral and bilateral neonatal RVT, respectively [21]. Renal vein thrombosis causing hypertension has been reported in older children and adults secondary to sepsis, burns, catheterizations, malignancies, antiphospholipid syndrome, and patients with the nephrotic syndrome [22, 23]. Renal vein thrombosis and associated pulmonary emboli have also been seen as the initial manifestation in patients with lupus nephritis [24]. Umbilical artery catheter placement in newborns may cause renal artery thrombosis (see Chap. 26).

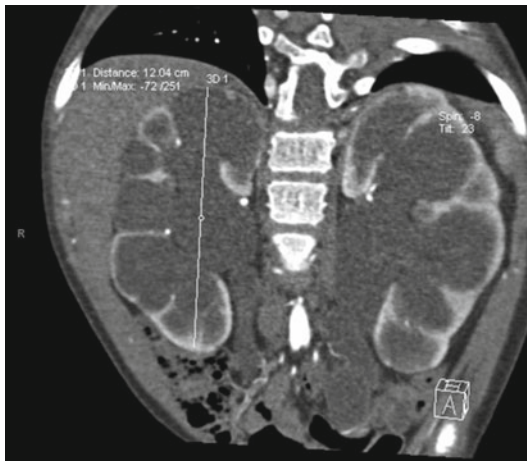

Fig. 21.3 Obstructive uropathy post-radiotherapy. Shown is severe bilateral hydronephrosis in an 18-year-old with bilateral ureteral stricture that occurred after radiation therapy to treat an infantile rhabdomyosarcoma

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. However, CoA is more likely to represent a spectrum of aortic narrowing from this discrete entity to tubular hypoplasia, with many variations seen in between these two extremes. The presence of arch hypoplasia is relevant to long-term risk of development of hypertension [25].

CoA is usually diagnosed in the newborn period or in infants; it is difficult to diagnose during fetal life due to the presence of the ductus arteriosus. It may also be discovered later in childhood and adolescence in association with upper limb BP elevation – an upper to lower limb BP gradient, ejection systolic murmur (ESM) that radiates to the back. CoA may be associated with bicuspid aortic valve, mitral/aortic stenosis, VSD, or PDA. For a discussion of management of CoA, please see Chap. 24.

An important point about CoA is that many patients have persistent hypertension at rest, during exercise, or both on long-term follow-up. Only a few patients develop restenosis (defined by a gradient of >20 mmHg) to explain persistence of

hypertension [26]. Persistent hypertension following CoA repair appears to be due to abnormalities in the arterial bed and its regulatory systems including increased sympathetic activity; there are reports of increased ventricular systolic stiffness coupled with increased arterial stiffness contributing to hypertension in patients with repaired CoA [27]. Early surgical intervention reduces the incidence of late hypertension, 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 needed.

Medication-/Drug-Related Hypertension

Stimulants for Attention Deficit Hyperactivity Disorder

Medications used to treat attention deficit hyperactivity disorder (ADHD) usually have a modest effect in increasing BP and heart rate. This effect was clearly demonstrated in several studies that utilized ambulatory BP [28–30]. 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. In children, average increases of 6–8 beats per minute in heart rate, 3–6 mmHg in systolic blood pressure, and 3–4 mmHg in diastolic blood pressure relative to placebo have been reported after methylphenidate or amphetamine administration [28, 31, 32]. On the other hand, central-acting alpha-blockers (clonidine, guanfacine) tend to both sedate and lower BP [33] and may therefore be used to counter the hypertensive effects of other medications used to treat ADHD.

Recreational Drugs

Cocaine and methamphetamines can cause hypertension and arrhythmias. Cocaine has been associated with accelerated and malignant hypertension as well as implicated in hastening the progression of hypertensive nephrosclerosis to ESRD [34]. The most common presenting symptom with cocaine abuse is chest pain. Cardiovascular complications related to cocaine include acute myocardial ischemia and infarction, arrhythmias, sudden death, myocarditis, cardiomyopathy, hypertensive crises, aortic dissection or rupture, and endocarditis.

Both cocaine and methamphetamines are sympathomimetic agents. They act by blocking the reuptake of norepinephrine and dopamine at preganglionic synaptic nerve endings. Hypertension associated with these substances is managed by withdrawal of the offending agent. Acute management of cocaine abuse includes supplemental oxygen, aspirin, nitroglycerin, benzodiazepines, and an alpha-blocker or calcium channel blocker to control blood pressure. Use of a beta-blocker is controversial as beta-blockers could decrease coronary blood flow, increase seizure risk, and thereby increase mortality [35]. Management of methamphetamine abuse includes benzodiazepines and haloperidol to calm the patient and beta-blockers to control blood pressure.

Oral Contraceptives

Oral contraceptives (OCPs) can induce or exacerbate hypertension. Contraceptive-associated hypertension is more likely to occur in women with a family history of hypertension [36]. The increase in BP is usually minimal; however, severe hypertensive episodes, including malignant hypertension, have been reported. The main pathophysiologic mechanism is an estrogen-mediated stimulation of the RAAS due to increased hepatic synthesis of renin substrate and, therefore, fluid retention due to increased sodium and water retention and peripheral vasoconstriction [37]. Use of an OCP with a lower estrogen dose may not cause hypertension as often, but may be less effective, especially in young women with significant dysmenorrhea. Progestin-only OCPs are unlikely to elevate BP but are associated with a greater incidence of spotting.

Over-the-Counter Medications

A number of over-the-counter (OTC) medications can lead to elevations in BP. For example, most nonprescription anorexics contain combinations of an antihistamine and adrenergic agonist (usually phenylpropanolamine [PPA], 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. Caffeine can also acutely and transiently increase BP by increasing peripheral resistance. The reaction to caffeine is more pronounced in males than females and in those with a positive family history of hypertension [38–40]. Concomitant use of other medications (monoamine oxidase inhibitors, oral contraceptives, and nonsteroidal anti-inflammatory drugs) seems to increase the risk of hypertension [41, 42].

Endocrine Causes of Hypertension

There are strong associations between glycemic control, BP regulation, and microalbuminuria in both type 1 and type 2 diabetes mellitus. The presence of nocturnal hypertension and loss of the nocturnal dip in BP appears to herald diabetic complications such as microalbuminuria [43, 44]. In addition to optimization of metabolic control, early diagnosis and prompt treatment of dyslipidemia and hypertension are important in patients with type 1 diabetes [45]. The American diabetes association (ADA) recommends measuring a child's BP at every diabetic visit to identify early hypertension or upward trends in BP and also recommends screening lipid levels in youth with T1DM at 12 years of age and every 5 years thereafter. If hypertension is documented, evaluation of the child should include updating parental history for hypertension, laboratory examination of renal function (urinalysis, serum creatinine, and blood urea nitrogen), and urinary albumin excretion.

The recommended treatment for hypertension in youth with TIDM initially is elimination of added salt in the diet and encouragement to exercise if the child is sedentary. Pharmacologic therapy is indicated if lifestyle intervention does not lead to adequate blood pressure improvement in 3–6 months in children with BP consistently over the 95th percentile. ACE inhibitors should be used with caution in adolescents and adequate counseling on using contraceptives should be provided [46]. As in adults, adolescents with type 2 diabetes also exhibit abnormalities of ambulatory BP, dyslipidemia, and microalbuminuria [47]. This is discussed in more detail in Chap. 19.

The main cause of morbidity and mortality in patients with type 1 diabetes is nephropathy, and the best marker in adults of the consequent risk of developing nephropathy is persistent microalbuminuria. Puberty represents the most important risk factor for the development of theses microangiopathic complications. Hypertension may also accelerate progression of vascular complications.

Other forms of endocrine hypertension are discussed in Chaps. 6 and 25, and hypertension in type 2 diabetes is discussed in Chap. 19.

Perinatal Causes of Hypertension

Events that take place in utero may affect blood pressure in both childhood and adulthood. These include low birth weight secondary to prematurity and causes of intrauterine growth retardation (maternal smoking, medications, poor nutrition, and infections) [48, 49]. Low birth weight and intrauterine growth restriction are associated with reduced nephron number. Moreover, excessive catch-up growth during the postnatal period results in increased metabolic demand on the kidney causing hyperfiltration leading to further nephron loss [50]. Other secondary neonatal causes of hypertension including renal artery/vein thrombosis, chronic lung disease, post-ECMO treatment, coarctation of aorta, and congenital renal malformations are discussed elsewhere in the text.

Central Causes of Hypertension

Central nervous system causes of hypertension include raised intracranial pressure secondary to space occupying lesion (tumors, abscess, or

hemorrhage), sympathetic nervous system abnormalities, and vasomotor center abnormalities that should be diagnosed prior to treating hypertension. While primary treatment is of the underlying condition, centrally acting alpha-blockers may be useful antihypertensive agents in some patients.

Miscellaneous Causes of Secondary Hypertension

Following Orthopedic Procedures

Hypertension in children and adolescents has been described with clubfoot repair, hip and knee contracture release, traction following pelvic fracture or congenital hip dislocation, immobilization of extremities following casting, and traumatic amputation [51–53]. 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 pain control and the use of diuretics, alpha blockade, and calcium channel blockers.

Environmental Exposures and Hypertension

Mercury and heavy metals can lead to hypertension. 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 United Kingdom and the United States until the late 1940s when it was realized that the condition was primarily caused by exposure to calomel (mercurous chloride) in teething powders and in anthelmintic preparations. Some sort of allergic reaction toward mercury in combination with a highly variable individual susceptibility are considered to be important pathogenetically; 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 %) [54]. Other heavy metal intoxications, including lead and cadmium, also have been associated with hypertension in children [55, 56].

Obesity: Is It Really Just Another Cause of Secondary Hypertension?

The prevalence of hypertension is threefold higher in obese children than in nonobese children. Blood pressure increase in children in the past decade is almost completely attributable to the increased prevalence of obesity [57, 58]. Childhood obesity is associated with established risk factors for cardiovascular disease including hypertension, diabetes, metabolic syndrome, and obstructive sleep apnea (OSA) and results in significant morbidity and mortality. 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 [59]. Visceral adiposity (waist circumference, waist/hip ratio) in adults predicts hypertension slightly better than BMI reflecting the strong relationship that visceral adiposity has with insulin resistance and endothelial dysfunction [60]. This association is also emerging in children [61]. Other factors that have been predictors of hypertension in adults include renal sinus fat volume independent of age, sex, BMI, and height [62] and nonalcoholic fatty liver disease and excessive fructose intake. Data in adolescents from NHANES corroborate this risk, with an approximately 2 mmHg difference in BP from the lowest to the highest strata of soda consumption [63].

Probable mechanisms of obesity-related hypertension include insulin resistance or hyperinsulinism causing an anti-natriuretic effect and increased sympathetic activity, activation of the RAAS, and altered vascular function [64]. With increasing obesity there is increased leptin,

resistin, IL-6, and TNF-alpha secretion; elevated free fatty acid release; and blunted production of adiponectin. A decrease in plasma adiponectin results in insulin resistance, decreased induction of endothelial nitric oxide synthase (eNOS), and possibly increased sympathetic activity. Resistin impairs nitric oxide synthesis (eNOS inhibition) and enhances endothelin-1 production, with its attendant vasoconstriction. Hyperleptinemia activates the sympathetic nervous system through complex mechanisms that involve central leptin receptors which lead to sodium retention [65].

Perhaps it is time to consider obesity as a secondary and independent cause of hypertension in children and adults.

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 that fail to show any correlation between adenotonsillar size and OSA severity, and by studies that show that tonsillectomy and adenoidectomy is not always effective in curing OSA [66]. Although studies in children are limited, the pathogenesis of OSA-related cardiovascular disease (Fig. 21.4) is thought to be due to interactions between hypoxemia from recurrent obstruction with resultant oxidative stress causing inflammation and endothelial dysfunction [67], increased nocturnal sympathetic activation as a consequence of multiple arousals (in response to obstructive events), increased mechanical load on the heart due to the generation of recurrent negative intrathoracic pressure, and metabolic dysregulation [68].

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 [69] or an increase of systolic BP with recurrence of OSA [70] or no change in BP after surgery [71]. However additional cardiovascular disturbances including increased sympathetic activity [72] and ventricular dysfunction have shown improvement after tonsillectomy and adenoidectomy [73]. In summary, it seems that early detection and management of OSA in children will improve BP and reduce later cardiovascular morbidity [74].

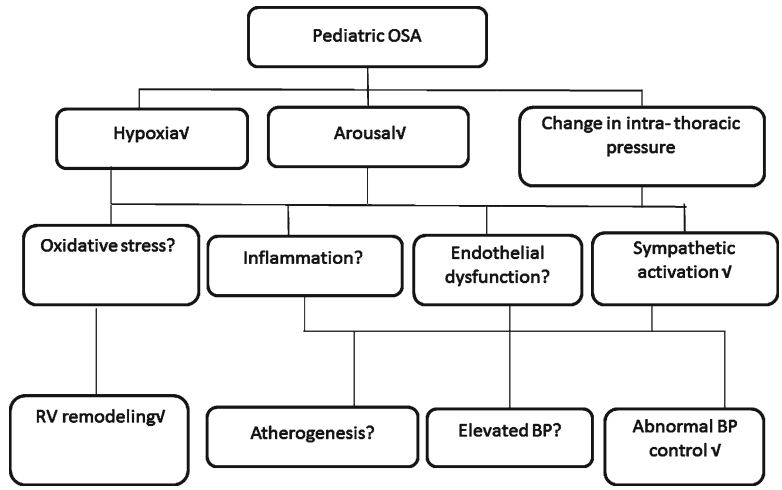

Fig. 21.4 Pediatric OSA. The figure shows the effects of treatment on the cardiovascular consequences of obstructive sleep apnea in children. The tick indicates studies that show improvement in the cardiovascular outcome with treatment; the question mark indicates study results are conflicting or that the treatment effects are unknown. *OSA* indicates obstructive sleep apnea, *RV* right ventricle, *BP* blood pressure (Used with reprint permission from Elsevier [58])

Approach to Asymptomatic Patients with a Normal Physical Exam

Trying to decide how far to investigate the asymptomatic otherwise normal child for secondary forms of hypertension can be both frustrating and perplexing. One approach is to consider whether there are specific features of the patient's history that may point the clinician either toward or away from secondary hypertension.

It would also be useful to identify certain factors that help to differentiate if an asymptomatic child has primary or secondary hypertension. Recent studies have identified that increased birth weight, rapid postnatal growth, and increased current weight were positive predictors of an increased risk for primary hypertension [75–77]. In another study, prematurity was considered as a determinant of developing primary hypertension, which was shown by the daytime systolic BP being higher in 50 adults born prematurely when compared with 30 full-term control adults [78]. In the Newcastle Thousand Families Study, with 412 adults between the ages of 49–51, birth weight was a statistically significant predictor of hypertension but was quantitatively much less important than BMI [79]. Thus, some of the clinical factors associated with primary hypertension include family history, low birth weight, prematurity, exposure to maternal smoking [80], hyperuricemia which is linked to increased consumption of fructose-containing beverages [81], accelerated skeletal maturation in adolescents independent of BMI [82, 83], and sleep-disordered breathing.

Baracco et al. identified a number of predictors for secondary hypertension in children; these include younger age – less than 12 years – elevated diastolic BP, and a discrepancy on ultrasound in the size of the kidneys of greater than 1.5 cm. 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 ACEi and diuretics).
- Urinalysis for proteinuria.
- Renal ultrasound for any scarring or structural abnormalities.
- 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 ACEi.
- No thyroid studies or urine catecholamines are recommended unless the patient is symptomatic [84].

Finally, specific patterns on ambulatory BP monitoring, including sleep hypertension and reduced nocturnal BP dipping, have also been associated with secondary hypertension in children [85, 86]. This is discussed in more detail in Chap. 11.

Based on the above results and risk factors, we suggest development of a "likelihood" table to help predict whether an asymptomatic child has primary hypertension or whether secondary hypertension should be considered more likely, thereby requiring further focused investigation (Table 21.3).

Table 21.3 "Likelihood factors" may help differentiate primary from secondary hypertension

	Predictors	1 HTN	2 HTN
1.	*Age*		
	5 to < 12 years	–	+
2.	*History*		
		Adult	*Child*
	Prenatal		
	Prematurity	+	+
	Low birth weight	+	+
	School age		
	Advanced postnatal weight gain	+	–
	Maternal smoking	+	–
	Puberty		
	Accelerated skeletal maturation	+	–
	Adolescent		
	Sleep-disordered breathing	+	–
	High fructose diet – hyperuricemia	+	–
3.	*BP*		
	Systolic HTN	+	–
	Diastolic HTN	–	+
4.	*Work-up*		
	Renal US: discrepancy in size of kidneys ≥ 1.5 cm	–	+

Conclusions

The etiology for a secondary cause of hypertension in children is not always obvious. In some children clues from history and examination will point toward 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.

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Hypertension in Chronic Kidney Disease

22

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Abstract

Renoparenchymal and renovascular disorders are the most common causes of secondary hypertension in childhood, accounting for 85 % of cases. The prevalence of hypertension in children with chronic kidney disease (CKD) is around 70 %, ranging from 50 % in mild to 80 % in severe CKD. The risk of hypertension is more closely associated with the type of underlying disease than with the degree of renal insufficiency; children with acquired glomerulopathies or polycystic kidney disease tend to have higher blood pressure than patients with renal hypoplasia and/or uropathies. Irrespective of the underlying kidney disease, hypertension and proteinuria are independent risk factors for renal disease progression. Thus, in order to prevent progression, therapeutic efforts should be directed not only to efficient control of blood pressure but also to maximal reduction of proteinuria.

Keywords

Hypertension • Chronic kidney disease • Children • Progression • Cardiovascular • Treatment • ACE inhibitor • Angiotensin receptor blocker • Pathophysiology

Abbreviations

4C	Cardiovascular Comorbidity in Children with CKD
ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin-converting enzyme
ACEi	Angiotensin-converting enzyme inhibitor
ADMA	Asymmetric dimethylarginine
Ang II	Angiotensin II
ARB	Angiotensin receptor blocker
BP	Blood pressure

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CKD	Chronic kidney disease
CKiD	Chronic kidney disease in children
ET-1	Endothelin-1
GFR	Glomerular filtration rate
GH	Growth hormone
IGF-1	Insulin-like growth factor 1
NO	Nitric oxide
NOS	NO synthase
RAAS	Renin-angiotensin-aldosterone system

Prevalence of Renal Hypertension in Childhood

Arterial hypertension is the earliest and most prevalent complication of pediatric CKD [1]. Large cross-sectional cohort studies examining casual blood pressures in children with CKD in Europe (4C Study), Canada [1], and the USA [2] found (controlled or uncontrolled) hypertension at 54–70 % prevalence. Office blood pressure (BP) was found elevated in 61 % of children with CKD stage 1 and in > 80 % in CKD stage 3–5 [1]. Even among patients receiving antihypertensive treatment, blood pressure was in the hypertensive range in 40–50 %.

However, office BP is limited in both sensitivity and specificity for the true prevalence of hypertension in CKD, which is best diagnosed by 24-h ambulatory blood pressure monitoring (ABPM). By ABPM, the overall prevalence of uncontrolled hypertension (irrespective of antihypertensive therapy) in pediatric CKD ranged between 27 % and 48 %. The fraction of children with elevated blood pressure who are not receiving antihypertensive treatment was between 21 % and 45 % ([3, 4] and unpublished results of 4C Study) (Table 22.1 and Fig. 22.1). White-coat hypertension is found in 2–23 % and masked hypertension (i.e., normal office but elevated 24-h blood pressure) in 7–38 % of children with CKD ([3, 5] and unpublished results of 4C Study).

Underlying Disorders

Renovascular Disease

Renovascular hypertension is defined as hypertension resulting from lesions that impair blood flow to a part, or all, of one or both kidneys [6, 7]. It accounts for about 10 % of pediatric patients (20 % of infants) presenting with persistent hypertension. Renal artery stenosis by fibromuscular dysplasia is the most frequent underlying disorder (70 %), affecting the main renal artery and/or, more commonly, intrarenal vessels [8]. Fibromuscular dysplasia occurs in familial traits

Table 22.1 Summary of ambulatory blood pressure findings in children with CKD

Study	N	Definition of hypertension	Hypertension (controlled or uncontrolled)	Uncontrolled hypertension	Elevated BP without antihypertensive treatment	White-coat hypertension	Masked hypertension
ESCAPE Network survey [4]	508	Diastolic BP ≥ 95th pct	46 %	30 %	45 %	–	–
ESCAPE trial [5]	118	CBP or daytime systolic BP > 95th pct	–	–	–	23 %	7 %
4C Study (unpublished data)	525	24 h MAP ≥ 95th pct	76 %	27 %	21 %	9 %	16 %
CKiD ' study [3]	366	ABPM load > 25 %	54 %	48 %	44 %	2 %	38 %

BP blood pressure, *CBP* casual BP, *MAP* mean arterial pressure, *pct* percentile, *ABPM* ambulatory blood pressure monitoring

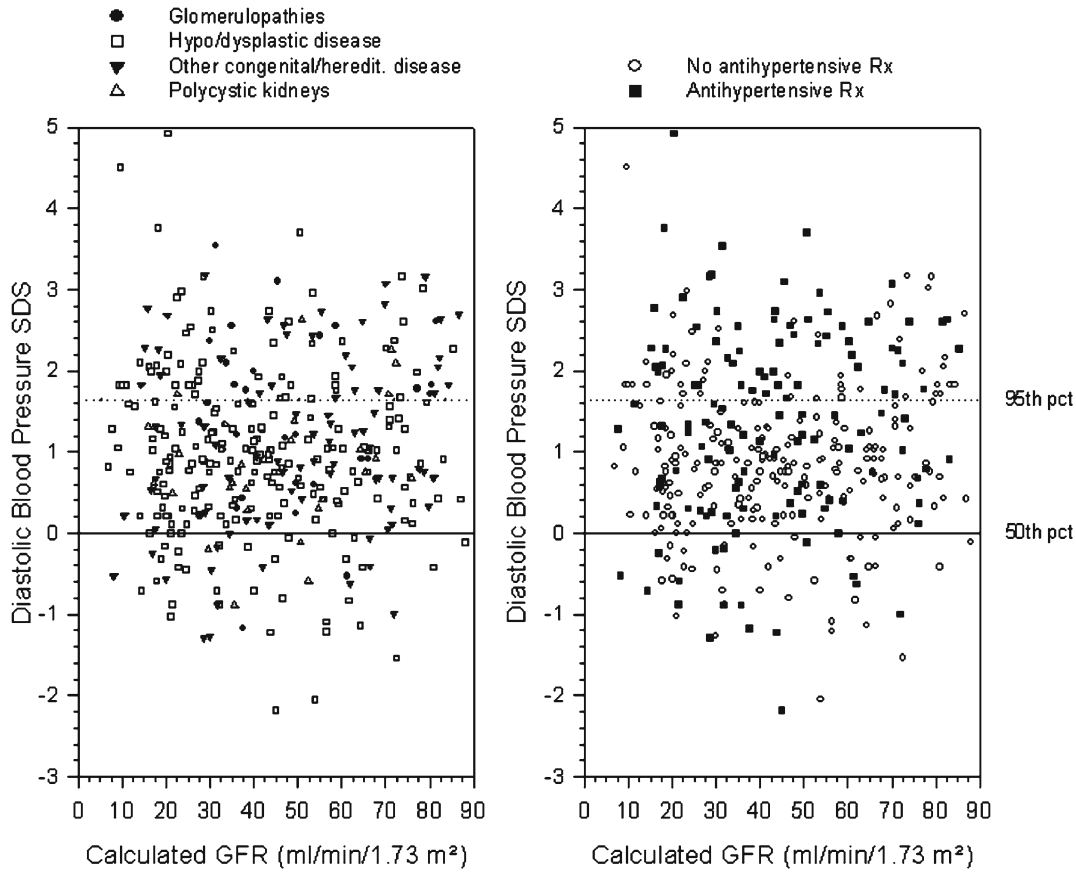

Fig. 22.1 Blood pressure in 508 children with chronic kidney disease. Distribution of diastolic blood pressure SDS is depicted according to underlying disease (*left panel*) and by prevalent antihypertensive medication (*right panel*). Data were obtained as part of a trial screening procedure in 33 European pediatric nephrology units (ESCAPE Network). Diastolic blood pressure values were converted to SDS using the European pediatric reference values for casual blood pressure of De Man et al. [158]

in the majority of cases [9]; the genetics are consistent with an autosomal-dominant inheritance with variable and often no clinical effect. Von Recklinghausen's neurofibromatosis constitutes a major subgroup among children with fibromuscular dysplasia, accounting for at least 15 % of all pediatric cases of renal artery stenosis [6, 10]. Another frequent genetic cause of renal artery stenosis is Williams-Beuren syndrome [11]. In these and other hereditary syndromes, renal artery stenosis is usually combined with anomalies of extrarenal arteries. The combination with aortic coarctation is known as the middle aortic syndrome [12]. Apart from vascular malformation complexes, renovascular hypertension is frequently caused by Takayasu disease, an unspecific aortoarteritis of autoimmune origin common in nonwhite populations [13]. Renovascular hypertension may also be due to other systemic vasculitic disorders, such as panarteritis nodosa or scleroderma. Renovascular causes of hypertension are discussed in more detail in Chap. 24.

Renoparenchymal Disease

Hypertension is very common in various forms of glomerulonephritis. Whereas acute, e.g., poststreptococcal, glomerulonephritis usually induces a reversible rise in blood pressure, chronic

glomerular disease is commonly associated with persistent hypertension. The most common underlying histopathological entities associated with hypertension even in the absence of renal failure are focal-segmental glomerulosclerosis, membranoproliferative glomerulonephritis, and crescentic glomerulonephritis. Persistent hypertension is also common in patients who recovered from hemolytic uremic syndrome. Moreover, a high prevalence of secondary hypertension is observed in glomerulonephritis secondary to systemic vasculitis, such as lupus erythematosus.

Renoparenchymal hypertension is not limited to glomerular disease, but is also observed in tubulointerstitial disorders leading to renal scarring. Recurrent pyelonephritis, reflux nephropathy, obstructive uropathies, and polycystic kidney disease all can lead to tubulointerstitial fibrosis and tubular atrophy. Scarring processes induce local renin and angiotensin synthesis, although systemic renin activity usually remains normal.

The risk of hypertension is more closely associated with the type of underlying disease than with the actual degree of renal dysfunction. At any given level of GFR, children with acquired glomerulopathies or polycystic kidney disease tend to have higher blood pressure than patients with renal hypoplasia and/or uropathies. In the survey of the ESCAPE trial group, the prevalence of hypertension was 88 % in patients with acquired glomerulopathies, 38 % in children with hypo-/dysplastic kidney disorders and 57 % in other congenital or hereditary renal diseases (Fig. 22.1). Renoparenchymal disorders overall are responsible for approximately 75 % of cases of secondary hypertension in childhood [14].

Pathomechanisms of Hypertension in Chronic Kidney Disease

Blood pressure can be elevated by an increase in cardiac output and/or of total peripheral resistance. Both mechanisms can be effected by a plethora of different mechanisms in CKD [15]. Figure 22.2 gives an overview of the most important pathways involved.

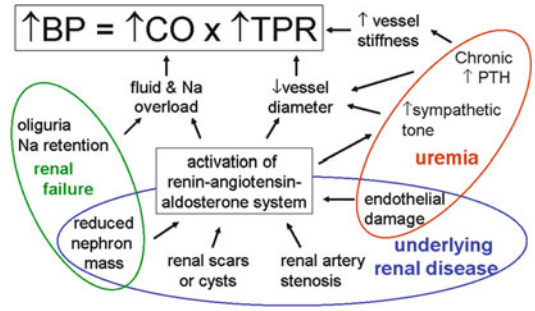

Fig. 22.2 Physiopathological mechanisms of hypertension in chronic kidney disease (From [15], with permission)

Sodium and Water Retention

Sodium retention and consequent fluid overload have long been recognized as a critical cause of hypertension in CKD. In a seminal study, Coleman and Guyton showed that infusion of normal saline in anephric dogs leads to hypertension characterized by an initial increase in plasma volume and cardiac output followed by an increased peripheral vascular resistance [16]. Extracellular fluid expansion is most consistently found in hypertensive ESRD patients. Hypertensive children on dialysis have lower residual urine output than their normotensive peers [17]. Strict enforcement of dry weight and normalization of sodium by reduced salt intake and slow long hemodialysis or additional ultrafiltration sessions have been shown to normalize blood pressure without the need for antihypertensives in adults and children [18, 19]. Plasma volume is elevated and correlated with blood pressure in renal disease, but not in primary hypertension.

On the other hand, the correlation between interdialytic weight gain and blood pressure is weak, suggesting that additional volume-independent mechanisms must also affect blood pressure in CKD [20–25]. Furthermore, the high prevalence of arterial hypertension in early CKD, when plasma and extracellular fluid volumes tend to be normal [26], supports a role of fluid-independent mechanisms. This is particularly remarkable in children with renal hypo-/dysplasia, who tend to lose considerable amounts of sodium

and water and yet are commonly hypertensive. The blood pressure-lowering efficacy of diuretics in early CKD is no proof for a leading role of salt and water retention in the pathogenesis of hypertension, since loop diuretics interfere with the vascular actions of angiotensin II (AngII) independent of their saluretic effect [27, 28].

The most compelling evidence for volume-independent mechanisms of hypertension in CKD comes from patients undergoing bilateral nephrectomy. In dialyzed children, nephrectomy lowers mean blood pressure despite causing anuria [29]. The removal of the native kidneys markedly reduces blood pressure and total peripheral vascular resistance, suggesting an excessive vasopressor function of failing kidneys. Of interest, previously hypertensive but not previously normotensive patients respond to salt and water loading by an increase of blood pressure. Hence, the vascular tone must be affected by kidney-related as well as kidney-unrelated mechanisms.

Renin-Angiotensin-Aldosterone System

Activation of the renin-angiotensin-aldosterone system (RAAS) plays a pivotal role in renal hypertension. While plasma renin activity is typically found markedly elevated only in patients with renal artery stenosis, many patients with CKD have "inappropriately normal" renin levels (i.e., lower levels would be expected considering their degree of hypertension and fluid overload [30, 31]). The infusion of normal saline fails to suppress plasma renin activity in patients with CKD stage 5 [31]. Hyperreninemia occurs probably due to renin secretion in poorly perfused areas such as cysts, scars, or after microangiopathic damage or tubulointerstitial inflammation [32, 33] and leads to Ang II-mediated vasoconstriction as well as aldosterone-mediated salt retention, thus increasing both total peripheral resistance and blood volume.

In addition to mediating systemic vasoconstriction and fluid retention, angiotensin is synthesized locally and regulates growth and differentiation in many tissues including the kidneys. The local angiotensin tone in the diseased kidney is affected by multiple mechanisms, independently of plasma renin activity. Locally formed Ang II increases transglomerular pressure and stimulates mesangial cell proliferation, glomerular hypertrophy, and tubulointerstitial fibrosis both directly and via regulation of growth factors and cytokines such as endothelin-1 and TGF-ß. Moreover, in CKD renal Ang II upregulates afferent neuronal activity originating from the kidney, contributing to sympathetic overstimulation. Additional delayed effects of a high local Ang II tone include microinflammation, cardiac hypertrophy, and endothelial cell damage [34]; these conditions further aggravate hypertension and end-organ damage.

Sympathetic Hyperactivation

Clinical and experimental evidence suggests that sympathetic overactivity may play a key role in the pathogenesis of hypertension in CKD. Sympathetic nerve activity is markedly increased in CKD and dialyzed patients [35, 36] and persists even after renal transplantation as long as the native kidneys are in place. After bilateral nephrectomy, sympathetic nerve activity normalizes, concomitantly with a reduction of blood pressure [35]. Treatment with ACE inhibitors, but not calcium channel blockers, normalizes sympathetic activity, suggesting an effect of the renal angiotensin tone on afferent neural signaling [36] (Fig. 22.2). The mechanisms underlying this phenomenon are as yet unclear and may include afferent signals from the failing kidney. In rodent models of acute and chronic renal disease, intrarenal afferent sensory neural pathways are activated which connect with the hypothalamic vasomotor control center, resulting in a rise in blood pressure sustained by noradrenergic mechanisms [37]. Renal denervation improves both hypertension and increased sympathetic activity [38]. In addition, abnormalities in dopaminergic neurotransmission and the accumulation of leptin have been postulated to be involved in CKD-associated sympathetic hyperactivation [39, 40]. Overactivation of the sympathetic drive

is also observed in renovascular and polycystic kidney disease-related hypertension [41], where renal afferent nervous input is probably triggered by renal ischemia.

An important role in the regulation of blood pressure and cardiac function has been attributed to renalase, an amine oxidase mainly expressed by the kidneys [42]. Renalase expression and enzymatic activity are rapidly turned on by modest increases in blood pressure and by brief surges in plasma catecholamines. The active enzyme degrades circulating catecholamines, causing a fall in blood pressure. The renalase knockout mouse (KO) is hypertensive and exquisitely sensitive to cardiac ischemia. Renalase expression is markedly deficient in animal models of CKD. Blood renalase levels are inversely correlated with glomerular filtration rate and are markedly reduced in patients with end-stage kidney disease. Renalase deficiency may thus contribute to the sympathetic overactivation, hypertension, and cardiac disease associated with CKD.

Endothelial Factors

The vascular endothelium exerts important endocrine and paracrine functions, including active control of the vascular tone. Endothelium-dependent vasodilation is impaired in CKD [43, 44].

The key vasodilatory factor secreted by the endothelium is nitric oxide (NO), the absence of which causes severe hypertension [45]. NO production is decreased in CKD [46, 47] as a result of impaired biosynthesis and bioavailability of L-arginine, reduced NO synthase (NOS) expression, and increased circulating endogenous NOS inhibitors [48]. Asymmetric dimethylarginine (ADMA), a potent NOS inhibitor, accumulates in CKD due to impaired renal excretion and enzymatic degradation. In hemodialysis patients, circulating ADMA concentrations are increased five- to tenfold [46, 49, 50]. ADMA independently predicts overall mortality and cardiovascular events in patients with ESRD as well as progression of CKD [51, 52], but these findings do not appear to be related to clinical differences in blood pressure [53]. A recent study in children with mild to moderate CKD showed no relationship of ADMA levels with 24-h blood pressure load. Moreover, the specificity of ADMA accumulation in uremia has been questioned, since ADMA is also elevated in patients with atherosclerotic disease and normal kidney function [50].

Endothelin-1 (ET-1), a peptide secreted mainly by vascular endothelial cells, is the most potent vasoconstrictor known to date. In addition, ET-1 affects salt and water homeostasis via interaction with the RAAS, vasopressin, and atrial natriuretic peptide and stimulates the sympathetic nervous system [54]. ET-1 overexpression renders mice susceptible to salt-induced hypertension and renal damage [55]. In the rat remnant kidney model of CKD as well as in ESRD patients, ET-1 plasma levels are increased in correlation with blood pressure [56]. Hence, circulating and possibly renal ET-1 may contribute to hypertension in CKD. Notably, ACE inhibitors reduce ET-1 expression and attenuate ET-1-induced hypertension by inhibiting the catabolism of vasodilatory kinins [57, 58].

Calcium and Parathyroid Hormone

Secondary hyperparathyroidism starts early in the course of CKD. PTH has multiple effects on the cardiovascular system. When infused acutely, PTH lowers blood pressure in a dose-dependent fashion via its well-established vasodilatory effect [59]. In contrast, a consistent positive correlation between blood pressure and serum PTH levels is observed in patients with chronic hyperparathyroidism [60]. Chronically elevated PTH leads to intracellular calcium accumulation in vascular smooth muscle cells, enhancing their sensitivity to calcium and norepinephrine [61, 62]. This effect can be blocked by calcium channel antagonists [62].

The enhancement of pressor responses by PTH and dysregulation of cytosolic calcium may be mediated in part via suppression of eNOS expression. In the remnant kidney rat model of CKD, reduced aortic eNOS protein abundance was observed, which could be reversed by parathyroidectomy and by calcium channel blockade [63].

Apart from PTH, cytosolic calcium is regulated by Na,K-ATPase. The activity of this transmembranous carrier protein is reduced in CKD by accumulated circulating digitalis-like substances, which may contribute to the proposed cytosolic calcium-mediated hyperresponsiveness of vascular smooth muscle cells to endogenous vasoconstrictors.

In addition, increasing evidence suggests that alterations of the complex endocrine network regulating bone-mineral metabolism, including PTH, vitamin D, FGF-23, and klotho, may contribute to impaired vascular function, in part via interaction with the RAAS [64]. FGF-23, in conjunction with its co-receptor klotho, physiologically stimulates phosphaturia and regulates alpha-hydroxylase activity. Active vitamin D generated by renal alpha-hydroxylase suppresses renal renin production. In uremia, low 1,25-OH vitamin D3 levels induce activation of the RAAS by upregulation of renal renin production [64]. Elevated FGF-23 levels in patients with CKD are associated with left ventricular hypertrophy and mortality [65]. Since klotho is involved in nitric oxide synthesis and endothelial function, the decreased klotho levels found in patients with CKD might contribute to endothelial dysfunction and hypertension. Preliminary evidence suggests that the klotho genotype is associated with blood pressure regulation and the responsiveness to antihypertensive treatment. Patients homozygous for the KL-VS variant in the klotho gene showed lower systolic blood pressure and pulse pressure and greater BP reduction upon antihypertensive treatment [66]. It should be noted though that despite these putative mechanistic links between FGF-23/klotho and vascular function, direct associations of FGF-23 or klotho levels with blood pressure regulation have not been demonstrated either in healthy subjects or in CKD patients to date.

Uric Acid

Serum uric acid is a major mediator of vascular damage in primary hypertension [67]. It is hypothesized that hyperuricemia leads to renal arteriolopathy and hypertension by activation of the RAAS, reduction of endothelial NO levels, and inhibition of endothelial and vascular smooth muscle cell proliferation [68]. With the generally increasing prevalence of obesity and metabolic syndrome, the role of uric acid has become a focus of interest as an additional pathogenic mechanism also in adults and children with CKD. Like in adult studies [69], an association between hyperuricemia and blood pressure has been demonstrated in the pediatric CKD population [70]. The epidemiological link of uric acid and hypertension may have been somewhat overestimated in earlier studies. A recent meta-analysis of 18 studies representing data from more than 50,000 patients suggested that young and female patients may be particularly prone to the hypertensiogenic effects of hyperuricemia [71]. The role of uric acid in the pathogenesis of hypertension is discussed in greater detail in Chap. 5.

Intrauterine Programming

Environmental influences in intrauterine life may predispose individuals to hypertension, dyslipidemia, and cardiovascular disease in later life (see also Chap. 7). Barker and coworkers first proposed that intrauterine malnutrition, indicated by low birth weight, is associated with type II diabetes mellitus, hypertension, dyslipidemia, and cardiovascular disease in adult life [72]. Furthermore, intrauterine malnutrition appears to be associated with reduced nephrogenesis. Maternal protein intake appears to be critical for fetal nephron endowment. Similarly, exposure to excess glucocorticoids leads to a decrease in nephron number by 30–40 % in rodents and sheep [73], associated with marked hypertension in postadolescent life.

A disproportionate reduction of kidney size suggesting reduced nephron mass is evident by ultrasound in children with intrauterine growth retardation antenatally and at birth [74, 75]. A possible link between reduced nephron endowment and the development of hypertension has been suggested by an autopsy study in subjects with primary hypertension and matched non-hypertensive controls, which disclosed a reduction in total

kidney nephron number by almost 50 % in the hypertensive subjects, which was compensated by a twofold increase in glomerular size [76]. While this observation appears compatible with the Brenner hypothesis, implying that a congenital reduction of nephron endowment predisposes to hypertension as a long-term consequence of glomerular hyperfiltration and glomerulosclerosis [77], glomerulosclerosis was very mild in the hypertensive oligonephronic humans and absent in the sheep model [73, 76]. Also, unilateral nephrectomy leads to hypertension only when performed during the period of active nephrogenesis in rats and sheep [78, 79], and children with unilateral renal agenesis have higher 24-h blood pressure than children losing one kidney shortly after birth [80]. Additional mechanisms of prenatal blood pressure imprinting have been suggested such as persistent upregulation of renal angiotensinogen and angiotensin receptors and increased sodium channel expression [81, 82], which may operate independently of nephron endowment. Hence, reduced renal mass and hypertension may not be causally linked, but both are secondary to intrauterine malnutrition. Finally, it is possible that abnormalities in genes controlling nephron development could also affect the predisposition for hypertension [83].

Pharmacological Hypertension

A number of drugs commonly administered in CKD can cause "iatrogenic" hypertension. Blood pressure elevation is commonly seen upon institution of *erythropoietin* (EPO) treatment, possibly due to arterial wall remodeling causing increased vascular resistance [84]. EPO may also act directly on voltage-independent calcium channels on smooth muscle cells, leading to a decreased sensitivity to the vasodilatory action of nitric oxide [85]. Calcium channel antagonist therapy as a mechanistically logical approach for EPO-induced hypertension has been successfully tested in the rat model [86].

Glucocorticoids lead to fluid retention by their mineralocorticoid effect. *Calcineurin inhibitors* cause vasoconstriction of glomerular afferent arterioles and hyperplasia of the juxtaglomerular apparatus with subsequent increased release of renin and Ang II [87]. Increased circulating catecholamines and endothelin-1 precursors and an increased renal sodium absorption via the Na-K-2Cl co-transporter in the loop of Henle [88] have also been demonstrated after cyclosporine A treatment. Tacrolimus appears to be somewhat less hypertensiogenic than cyclosporine A at bioequivalent doses [89]. Treatment with *growth hormone* leads to water and sodium retention by the distal nephron [90] mediated by increased intrarenal IGF-1. However, GH does appear to not increase blood pressure in children with CKD [91].

Hypertension and Progression of Chronic Renal Failure

A large body of evidence from epidemiological studies and clinical trials indicates that hypertension is an important risk factor for progressive renal disease. In the Multiple Risk Factor Intervention Trial (MRFIT) which followed more than 330,000 men over up to 16 years, the initial blood pressure level predicted the risk of developing end-stage renal disease; even blood pressure in the high-normal range was associated with a twofold renal risk [92]. Numerous interventional trials have demonstrated that lowering blood pressure preserves kidney function in hypertensive patients at risk for progressive renal disease (Table 22.2) [93–105].

Besides hypertension, proteinuria is a major risk factor for renal failure progression. Although hypertension aggravates proteinuria and the two risk factors are strongly interrelated, they independently impact on renal survival. Two prospective pediatric trials have demonstrated that hypertension and proteinuria are major independent risk factors for progressive renal failure also in children with CKD [94, 106] (Fig. 22.3). In the following, we will discuss the pathomechanisms by which hypertension and proteinuria contribute to renal disease progression and the resulting concepts of pharmacological nephroprotection in children with CKD.

Table 22.2 Randomized clinical trials demonstrating renoprotective effect of antihypertensive treatment (See text for details. Adapted from Toto [154])

Source	Patient population	Renal outcome	ACEI-ARB comparison versus other AHT	ACEI/ARB superior
Parving et al. [145]	Type 1 DM	Slowed decline in GFR	No	–
Peterson et al. [93]	Nondiabetic	Slowed decline in GFR	No	–
Lewis et al. [97]	Type 1 DM	Decreased risk for ESRD, doubling SCr, and death	Yes, ACEI	Yes
Bakris et al. [103]	Type 2 DM	Slowed decline in GFR	Yes, ACEI	Yes
UK Prospective Diabetes Study group [105]	Type 2 DM	Decreased risk of proteinuria	Yes, ACEI	No
Zucchelli et al. [100]	Nondiabetic renal disease	Slowed decline in GFR	Yes, ACEI	No
Hannedouche et al. [101]	Nondiabetic renal disease	Slowed decline in GFR	Yes, ACEI	No
Kamper et al. [98]	Nondiabetic renal disease	Slowed decline in GFR	Yes, ACEI	Yes
Toto et al. [95]	Hypertensive nephrosclerosis	Slowed decline in GFR	Yes, ACEI	No
Ihle et al. [102]	Nondiabetic renal disease	Slowed decline in GFR	Yes, ACEI	Yes
Maschio et al. [96]	Nondiabetic renal disease	Decreased risk for ESRD	Yes, ACEI	Yes
GISEN Group [104]	Glomerulonephritis	Decreased risk for ESRD	Yes, ACEI	Yes
AASK Group [119]	Nondiabetic renal disease	Decreased risk for ESRD, 50 % GFR loss, and death	Yes, ACEI	Yes
Parving et al. [155]	Type 2 DM	Decreased risk of proteinuria	Yes, ARB	Yes
Lewis et al. [156]	Type 2 DM	Decreased risk for ESRD, doubling SCr	Yes, ARB	Yes
RENAAL Group [157]	Type 2 DM	Decreased risk for ESRD, doubling SCr	Yes, ARB	Yes
Wühl et al. [94]	Children with CKD	Decreased risk for ESRD, 50 % GFR loss	Fixed-dose ACEI in all patients; intensified BP control by non-RAAS agents	–

ACEI indicates angiotensin-converting enzyme inhibitor, *ARB* angiotensin type I receptor blocker, *AHT* antihypertensive agents, *DM* diabetes mellitus, *GFR* glomerular filtration rate, *ESRD* end-stage renal disease, *SCr* serum creatinine; nondiabetic renal disease includes patients with hypertensive nephrosclerosis, glomerular disease, tubulointerstitial diseases, and autosomal-dominant polycystic disease

Pathomechanisms of CKD Progression

The current concepts of the mechanisms leading to progressive renal failure are summarized in Fig. 22.4. Healthy kidneys protect their glomerular tufts from the effects of systemic blood pressure variations by judicious adaptation of the afferent arteriolar tone, leading to a stable filtration pressure over a wide range of systemic BP. This autoregulation is thought to be defective in CKD [107], resulting in unrestrained transmission of systemic blood pressure to the glomeruli. Hypertension and preexisting renal damage converge on the level of glomerular transcapillary pressure. According to the Brenner hypothesis, any critical reduction of functional renal mass leads to hyperfiltration and intraglomerular hypertension in the remaining nephrons [77]. The increased filtration pressure causes, or aggravates

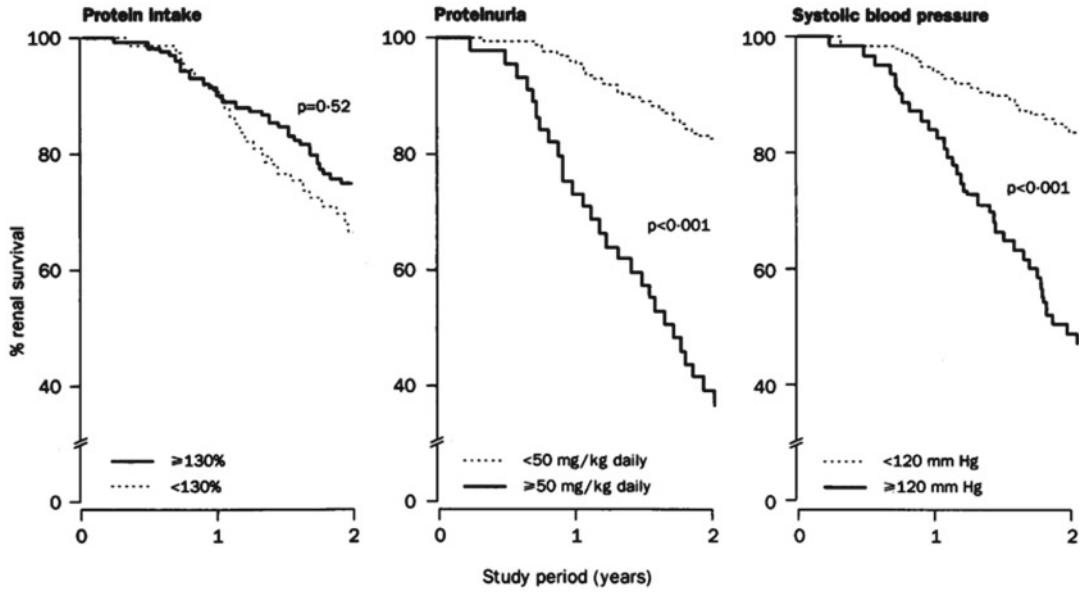

Fig. 22.3 Lack of beneficial effect of restricted protein intake on renal survival (defined as less than 10 ml/min/1.73 m^2 GFR loss during 2 years of observation) in 200 children with CKD (*left panel*). Secondary analysis revealed markedly poorer renal survival in children with proteinuria > 50 mg/kg per day (*middle panel*) and systolic blood pressure greater than 120 mmHg (From [106], with permission)

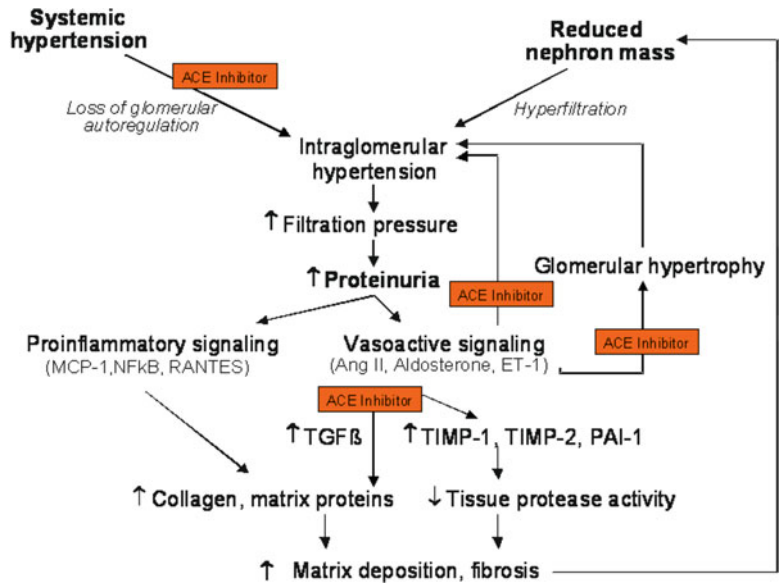

Fig. 22.4 Mechanisms of disease progression in CKD and sites of action of ACE inhibitors (See text for detail)

preexisting, proteinuria. The exposure of tubular and mesangial structures to macromolecular proteins elicits a marked and persistent tissue response. This is characterized by the release of vasoactive peptides and growth factors such as Ang II, endothelin-1, and others [108], which further increase intraglomerular hypertension by preferentially constricting the efferent arterioles and/or by inducing glomerular hypertrophy.

Independently of its glomerular hemodynamic effects, Ang II interferes with tubulointerstitial tissue homeostasis. Ang II stimulates the synthesis and release of TGF-ß which, via its downstream mediator connective tissue growth factor (CTGF), stimulates collagen and matrix protein synthesis. In addition, angiotensin and aldosterone induce the local release of inhibitors of tissue proteases such as TIMP-1, TIMP-2, and PAI-1. Increased production and diminished degradation of matrix proteins result in excessive deposition of fibrous filaments. Moreover, proteinuria and enhanced Ang II formation stimulate the synthesis and release of several proinflammatory cytokines and chemokines such as RANTES and MCP-1 and of the transcription factor NFkB [109, 110]. These mediators enhance macrophage infiltration, matrix deposition, interstitial fibrosis, and tubular cell apoptosis. In addition, proteinuria induces complement activation and oxidative stress to the tubular epithelial cells [111–113]. Another possible mechanism of progressive renal damage has been identified in animal models of hypertensive glomerulopathy [114]. Once glomerulosclerosis is established, synechial glomerular capillaries may continue to produce ultrafiltrate which is misdirected into the paraglomerular and peritubular space, resulting in a local inflammatory and fibrotic tissue response and atrophy of the nephron.

Antihypertensive and Nephroprotective Treatment Strategies in CKD

The epidemiological evidence and pathophysiological insights described above have stimulated the search for rational management strategies of CKD-associated hypertension. These relate to both blood pressure targets and preferred antihypertensive choices.

BP Target

For adult patients with CKD due to diabetic or nondiabetic nephropathies, meta-analyses of antihypertensive trials showed an almost linear relationship between achieved blood pressure and the rate of GFR loss [115].

Consequently, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) has recommended a blood pressure goal of <130/80 mmHg in patients with CKD or diabetes, as compared to <140/90 mmHg in hypertension of other origin. This was despite the fact that controlled randomized trials have not unanimously confirmed renoprotective superiority of very strict blood pressure control in patients with adult nephropathies.

In the MDRD trial, proteinuric patients randomized for a low blood pressure goal (<120/75) showed improved long-term renal survival over up to 10 years [116, 117], but this may have been biased by the preferential use of ACE inhibitors in the intensified treatment arm. In the REIN-2 trial, additional BP lowering targeting to <130/80 mmHg by addition of felodipine to ramipril did not improve renal survival [118]. In the AASK trial, forced blood pressure lowering to 92 mmHg mean arterial pressure in African Americans with hypertensive nephrosclerosis did not affect the rate of GFR loss [119]. In the ABCD trial, a lower blood pressure target did not improve renal survival in hypertensive diabetic patients, whereas normotensive patients benefited from lowering blood pressure to the low-normal range [120]. Thus, the wisdom of lower BP targets in adults with CKD has recently been questioned, and these lower targets may no longer be recommended by consensus organizations.

In children with CKD, the Efficacy of Strict Blood Pressure Control and ACE inhibition in Renal Failure Progression in Pediatric Patients (ESCAPE) trial has provided evidence for a nephroprotective effect of intensified blood pressure control [94]. Children randomized to a target

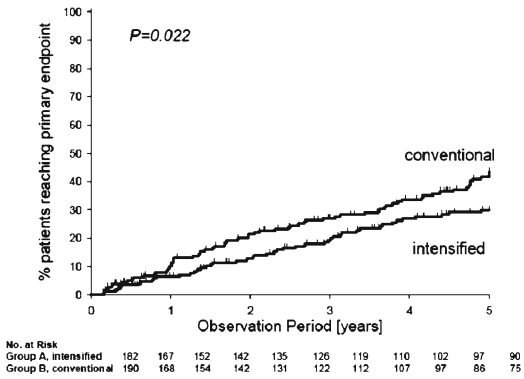

Fig. 22.5 Improved renal survival by intensified blood pressure control, targeting at 24-h mean arterial pressure below 50th percentile for age, sex, and height, in children with CKD (ESCAPE trial) (From [94], with permission)

Table 22.3 Likelihood of losing >50 % GFR or progressing to end-stage renal disease by achieved 24-h MAP in children with CKD. Renal survival benefit was statistically significant for any arbitrary cutoff blood pressure criterion down to the 50th percentile [94]

A 5-year renal survival in %			
Achieved BP	Below	Above	*p*
25th pct	66.3	66.8	0.63
50th pct	73.6	57.3	0.005
75th pct	70.1	49.9	0.001
90th pct	70.7	29.2	<0.001
95th pct	71.1	16.4	<0.001

24-h mean arterial pressure (MAP) below the 50th percentile for age were 35 % less likely to lose 50 % GFR or progress to end-stage renal disease within 5 years than children with a more conventional blood pressure target between the 50th and 95th percentiles of 24-h MAP (Fig. 22.5). The renal protective effect of low-normal BP was independent of RAAS inhibition since all subjects received the same dose of the ACE inhibitor ramipril. While the benefit was most pronounced in children with glomerular disorders, it was also significant in children with renal hypodysplasia, the most common cause of CKD in children. Survival analysis stratified by the achieved 24-h blood pressure throughout the 5-year observation period suggested that any blood pressure exceeding the 50th percentile was associated with a compromised renal outcome (Table 22.3). Proteinuria was an important modifier of the renoprotective efficacy of intensified BP control. The improvement of renal survival by intensified BP control was mainly explained by patients with significant proteinuria.

Apart from the renoprotective effect of intensified BP control, preliminary evidence from the ESCAPE trial suggests that BP reduction to the low-normal range is associated with regression of left ventricular hypertrophy in children with CKD, although no linear relationship between BP reduction and LVH regression was observed [121, 122]. Altogether, the results of the ESCAPE trial provide a rationale for targeting the 50th 24-h BP percentile in proteinuric and at least the 75th percentile in non-proteinuric children with mild to moderate CKD.

Choice of Antihypertensive Drugs

The multiple mechanisms by which Ang II is involved in renal failure progression provide a rationale for the hypothesis that RAAS antagonists might confer specific nephroprotection beyond their antihypertensive properties. RAAS antagonists lower transglomerular pressure and proteinuria and suppress local growth factor, cytokine, and chemokine release, with subsequent reduction of glomerular hypertrophy and sclerosis, as well as tubulointerstitial inflammation and fibrosis [94] (Fig. 22.4). To date, most albeit not all randomized clinical trials have demonstrated superior renoprotective efficacy of RAAS antagonists (ACE inhibitors (ACEi) and angiotensin type I receptor blockers (ARBs) alike) in adults with diabetic and nondiabetic CKD.

Several meta-analyses have confirmed the specific nephroprotective benefit of RAAS antagonists, although the effect size is somewhat controversial [123, 124]. One analysis suggested that the renoprotection conferred by ACEi may in part be independent of their antihypertensive and even of their antiproteinuric action [123]. RAAS antagonists are therefore considered the pharmacological option of first choice in hypertensive CKD patients and are even indicated in non-hypertensive patients with proteinuric, progressive CKD. In the CKiD study, an increased prevalence of uncontrolled hypertension was

found in CKiD participants not receiving ACEi or ARBs, lending additional support to the preferential use of RAAS antagonists in pediatric CKD [2].

Published information regarding the use of RAAS antagonists for BP control and nephroprotection in children with CKD includes small uncontrolled studies showing stable renal function in post-HUS children during long-term ACE inhibition [125], stable GFR during losartan treatment in children with proteinuric CKD [126], and attenuated histologic progression in children with IgA nephropathy receiving combined RAAS blockade [127]. Furthermore, the ESCAPE trial demonstrated efficient BP and short-term proteinuria reduction by the ACE inhibitor ramipril in 400 children with stage 2–4 CKD [128]. The drug was very well tolerated throughout 5 years of follow-up, with only 6 % of patients requiring discontinuation due to acute increases of serum creatinine (n=12), hyperkalemia (n=9), or hypotensive episodes (n=2) [94]. However, it was not possible to assess the effect of ACE inhibition on long-term GFR preservation in this trial since all subjects received ramipril at the same fixed dose.

The adult study populations in which the concept has been established mainly comprised patients with acquired glomerulopathies. In children, hypo-/dysplastic renal malformations and other congenital or hereditary disorders predominate. It could be argued that hyperfiltering nephrons in renal hypoplasia should be susceptible to the specific renal effects of RAAS inhibition. Hypertension and proteinuria clearly predict CKD progression also in children [106], and extensive tubulointerstitial fibrosis is commonly found in progressive pediatric nephropathies such as obstructive and refluxive nephropathies and nephronophthisis. These arguments provide a rationale for pharmacological renoprotection by RAAS inhibition in children with CKD. However, individual subsets of pediatric kidney disease may remain unresponsive to RAAS inhibition. Of note, polycystic kidney disease is the only disease entity identified to date in which ACE inhibition has not proven renoprotective [129].

There is some evidence suggesting that the RAAS is incompletely suppressed by ACE inhibition alone, and the possibility of partial secondary resistance due to compensatory upregulation of ACE-independent Ang II production has been suggested ("aldosterone escape") [130–132]. In the pediatric ESCAPE trial, proteinuria was initially reduced by ACE inhibition by about 50 % [128]. However, proteinuria subsequently gradually rebounded to pretreatment levels within 3 years despite ongoing ramipril therapy, continued suppression of circulating ACE activity, and persistently excellent blood pressure control [94]. Since residual protein excretion on treatment was predictive of renal survival, breakthrough proteinuria may limit the long-term therapeutic benefit of ACE inhibition in CKD.

In theory, breakthrough proteinuria should not occur with drug classes blocking the RAAS further downstream such as ARBs or aldosterone receptor blockers. Recent research suggests that the doses required to achieve the maximal antiproteinuric effect of ARBs may be much higher than the maximally active antihypertensive doses. Significant additional proteinuria lowering was achieved without increased side effects in adults by 64 and even 128 mg of candesartan, which has no additional blood pressure-lowering effect beyond daily doses of 16–32 mg [133]. Hence, ARBs and potentially selective aldosterone receptor blockers such as eplerenone, dose titrated to maximal antiproteinuric action, may become the first-line pharmacological approach in proteinuric CKD.

Aliskiren, a direct renin antagonist blocking the conversion from angiotensinogen to angiotensin I, effectively lowers blood pressure in animals and humans. The blood pressure-lowering effect is quantitatively comparable to that of ARBs, and combination therapy of aliskiren and valsartan at maximum recommended doses provides significantly greater blood pressure reduction than the respective monotherapies [134]. However, combination therapy of aliskiren with ACEi or ARBs significantly increased the risk of cardiovascular events in patients with diabetes or

CKD in the ALTITUDE trial and is currently not recommended [135].

Proteinuria can also be minimized by combined use of ACEIs and ARBs [136–138]. Whereas an earlier randomized trial had suggested improved renal survival with ACEI-ARB combination therapy [136], a trial in 28,000 patients showed no better patient or renal survival and slightly increased incidences of hyperkalemia and acute renal failure in patients with high cardiovascular risk on combined high-dose ramipril and telmisartan as compared to monotherapies [139, 140]. Hyperkalemia is also the limiting factor for combinations of ACEIs with mineralocorticoid receptor blockers [141].

In the ESCAPE trial blood pressure control (24-h MAP <95th percentile) was achieved with ACE inhibitor monotherapy in only 57 % of children. Intensified BP control was achieved in two third of patients in the intervention arm; this was accomplished by ramipril alone in 52 % and by combination therapy (1.5 additional drugs on average) in 47 % of patients [94]. Hence, a significant number of pediatric CKD patients require multidrug antihypertensive therapy. The choice of additional antihypertensive drugs in children with CKD is largely arbitrary. Dihydropyridine calcium channel blockers have no antiproteinuric effect and may actually promote proteinuria and more rapid CKD progression [142]. However, their combination with ARBs or ACEi provides very powerful blood pressure lowering and even conferred a patient survival advantage as compared to the combination of ARBs or ACEi with thiazide diuretics [143, 144].

Non-dihydropyridine calcium channel blockers (diltiazem, verapamil) are antiproteinuric and therefore potentially renoprotective, but have a weaker effect on blood pressure [142].

The use of ß-receptor blockers appears rational in view of the sympathetic overactivation in CKD. Metoprolol and atenolol were the first antihypertensive drugs used to demonstrate nephroprotective effects of good blood pressure control [145]. Newer β-blockers, e.g., carvedilol, exert a significantly greater antiproteinuric effect than atenolol at comparable blood pressure reduction [146, 147].

Timing of Medication Dosing

One of the characteristic features of renal hypertension is the loss of the physiological nocturnal decrease in blood pressure (dipping). Bedtime dosing of antihypertensive medication tends to restore the circadian blood pressure rhythmicity by a more marked pharmacodynamic effect during the nighttime hours. A recent study in 661 adult CKD patients randomly assigned either to take all antihypertensive medication in the morning or to take at least one drug in the evening, bedtime dosing not only improved overall blood pressure control but also reduced the risk for cardiovascular events (composite endpoint of cardiac death, myocardial infarction, or stroke) by 72 % [148].

Secondary Complications of Hypertension in Pediatric CKD

Cardiovascular Disease

Left ventricular hypertrophy (LVH) and abnormal cardiac function are common in patients with CKD. One third of the children with mild to moderate CKD undergoing echocardiography in the ESCAPE trial exhibited LVH at study entry. The prevalence of LVH ranged between 17 % and 38 % in large cohort studies encompassing more than 1,200 children with CKD (ESCAPE, CKiD, 4C) [3, 149, 150].

Hypertension is the major, albeit not the only, risk factor contributing to LVH in CKD. In the CKiD cohort, not only children with overt office and 24-h hypertension but also those with masked hypertension were at increased risk of LVH [3].

LVH appears to be readily responsive to effective antihypertensive therapy. In the ESCAPE trial, treatment according to the study protocol, i.e., fixed-dose ACE inhibition with or without additional BP-lowering medications, decreased LVH prevalence from 38 % to 25 % and improved systolic function within 12 months [149].

Neurocognitive Function

Both children with CKD and those with primary hypertension are at increased risk for neurocognitive dysfunction [151, 152]. To evaluate the role of hypertension in neurocognitive dysfunction in children with CKD, 383 CKiD participants underwent Wechsler Abbreviated Scales of Intelligence (WASI) Performance IQ assessments. The 132 children with elevated blood pressure had significantly lower mean scores than those with normal blood pressure [153]. Effective blood pressure control improves neurocognitive function in children with primary hypertension [152]; whether similar effects can be achieved in hypertensive children with CKD will need to be addressed in prospective interventional trials.

Conclusions

Hypertension is extremely common in children with CKD and contributes to progression of CKD by a variety of mechanisms, with the RAAS playing a central role. Given the beneficial effects of BP reduction in hypertensive adults with CKD and the demonstrated slowing of progression of pediatric CKD with intensified BP control in the ESCAPE trial, antihypertensive treatment is paramount to slowing CKD progression. ABPM-guided treatment to a 24-h MAP below the 50th percentile for age would appear to be the best strategy to achieve maximal nephroprotection. Available evidence suggests that an agent affecting the RAAS should be the initial medication chosen, with other classes of antihypertensive agents added as needed until the child's BP is controlled. Combinations of different RAAS agents may be needed to achieve maximal BP reduction and control of proteinuria, but these combinations require further study in the pediatric age group.

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Hypertension in End-Stage Renal Disease

23

Tomáš Seeman

Abstract

Hypertension (HTN) is a frequent finding in children with end-stage renal disease (ESRD), occurring more often than in children with preterminal chronic kidney disease (CKD). The origin comes from the chronically diseased kidney (see preceding chapter), but additional risk factors may appear in dialyzed and transplanted children, including fluid overload, immunosuppressive drugs, and/or obesity. HTN is one of the most important risk factors for cardiovascular morbidity and mortality in children with ESRD. Furthermore, cardiovascular events are the most common cause of death in these patients. Therefore, the treatment of HTN is one of the most important strategies in dialyzed and transplanted children to improve their survival.

Keywords

Hypertension • Blood pressure • End-stage renal disease • Children • Dialysis • Kidney transplantation • Cardiovascular morbidity and mortality • Left ventricular hypertrophy

Hypertension in Children on Dialysis

Measurement of Blood Pressure in Dialyzed Children

Casual Blood Pressure

The same guidelines for measuring blood pressure (BP) used for normal children (see Chap. 25, Diagnostic Evaluation of Pediatric Hypertension) apply to children on peritoneal dialysis (PD). However, in measuring BP in children on hemodialysis (HD), the general rule to use the right

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upper extremity must often be disregarded if a right-arm arteriovenous fistula or graft is present because compression of the fistula or graft may contribute to access failure. Therefore, BP should be measured in the arm without a vascular access. In order to avoid difficulties in measuring BP in the upper extremities with arteriovenous fistulas, some authors proposed to use the legs to measure BP. However, systolic BP readings from the dorsalis pedis artery have yielded values 15 mmHg higher than arm pressures [1] and therefore are not comparable. Blood pressure measurement obtained in the thigh gives also higher BP values than in the arm [2]. The desired method of BP measurement in children still remains auscultation. Automated oscillometric BP monitors are increasingly used also in dialyzed children; however, they should be used and obtained values interpreted with caution because they give significantly higher BP values than auscultatory devices in adults as well as in children [3-5].

Controversies still exist surrounding the timing of BP measurement in HD patients. Casual readings are usually taken immediately after the start of the HD session, but this so-called predialytic BP overestimates the mean systolic interdialytic systolic BP by 10 mmHg, whereas the postdialytic BP may underestimate it by 7 mmHg in adult patients [6]. Similarly, predialytic BP is 6–9 mmHg higher than postdialytic BP in children [7]. Some authors believe that postdialytic readings better reflect the interdialytic BP [8], whereas others prefer predialytic BP as a guide for treatment [9]. Using postdialytic BP instead of predialytic BP for definition of HT in dialyzed children led to reclassification from HTN to normotension in only 8 % [7]. Predialytic BP has been shown to be the weakest predictor of left ventricular hypertrophy in adults [10].

Unfortunately, similar data are lacking in children. A variety of influences account for these BP differences, including changes in volume, neural signaling, local and systemic hormonal release, and vascular tone. Therefore, a composite of BP measurements over a period of several weeks rather than isolated readings during one HD session (predialytic or postdialytic BP) should be used for guidance [11]. Volume-related differences might be present also between morning and evening BP in patients undergoing automated overnight PD with significant ultrafiltration.

Ambulatory Blood Pressure

Ambulatory BP monitoring (ABPM) improves the evaluation of the BP status in HD as well as in PD patients. The many advantages of ABPM (see Chap. 29, [12]) are particularly evident in ESRD patients. The main advantage of ABPM, the possibility to evaluate nocturnal BP and circadian changes of BP, is particularly important in ESRD patients, in view of the prognostic significance of nocturnal dipping as dialyzed non-dipper patients have higher cardiovascular morbidity and mortality [13] and children with LVH have lower dipping than those without LVH [14]. Furthermore, the results of ABPM correlate also in dialyzed adults and children better with markers of target-organ damage, such as left ventricular hypertrophy, than of casual BP [14-16].

White-coat HTN and the white-coat effect play a more minor role than in other patient groups in adults [17]. Conflicting data on white-coat HTN exists in dialyzed children. Koch et al. showed no white-coat HTN, whereas Lingens et al. showed 31 % of dialyzed children whose casual BP values were in the normotensive range were reclassified as normotensive using ABPM [18, 19]. A relatively new phenomenon of masked HTN (normal CBP but elevated daytime ambulatory BP) is more prevalent than white-coat HTN in dialyzed children being detected in 12 % of them [14]. Studies in adult HD patients have shown that ABPM is relatively reproducible and less variable than casual pre- or postdialytic BP; however, the reproducibility of the BP decrease during sleep (nocturnal dip) is poor because up to 43 % of patients change their nocturnal dip category after repeated measurements [20]. This reflects many influences that affect circadian BP patterns in dialyzed patients and that change with time (e.g., changes in body volume and sodium that affect the nocturnal BP dip). The issue of reproducibility of nocturnal dip has not yet been studied in dialyzed children. Interdialytic weight gain has been shown to correlate with ambulatory BP in children in one study [17];

however, another study failed to demonstrate any correlation between interdialytic weight gain and BP [14]. Therefore, this issue deserves further investigation.

In dialyzed children, casual BP measurement and ABPM results are poorly correlated. A third of children appearing normotensive by casual readings have to be reclassified to hypertensive when examined by ABPM or the converse [19]. Sorof et al. [21] found a wide range of error for casual BP relative to ABPM, confirming the unreliable character of casual readings. Interdialytic BP monitoring with an ABPM monitor is therefore the most reproducible method and is thought to best represent BP in dialysis patients [11].

Home Blood Pressure

Home BP measurements obtained regularly by the patients or their parents have been shown to give lower values than clinic BP in most children [22]. It is an important method for control of HTN in dialyzed children and a valuable supplement to ABPM that can also increase the compliance of patients with antihypertensive therapy.

Definition and Prevalence of Hypertension in Dialyzed Children

Since children with ESRD are often growth retarded, problems with the definition of HTN may occur because no normative data for casual BP are available for children with heights below the 5th percentile [23] and since available normative data for pediatric ABPM, while indexed to height in centimeters, do not exist for children with heights <120 cm [24, 25]. Therefore, normative data for casual BP should be taken for the 5th–95th height percentile only even in children with heights below the 5th or above the 95th percentile [23] and normative data for ABPM for the patient's height regardless of the patient's age [24]. Extrapolation of ambulatory BP thresholds from the Soergel study [25] or use of data from small studies in young healthy children [26, 27] can be done in children with height <120 cm.

In general, casual BP readings in dialyzed patients are subject to sampling errors, mainly because of the great influence of the rapidly changing volume status (as previously noted). Even repeated casual measurements are not able to reflect circadian changes. It appears that in all ESRD patients, HTN can be better defined by applying ABPM than by casual recordings.

The reported prevalence of HTN in dialyzed children varies significantly in published studies, mainly depending on the method of BP measurement and the time of BP measurement in the different trials. In the first weeks or months after the start of dialysis therapy, BP tends to decrease and often allows reduction in antihypertensive medication [28]. However, HTN persists in a high proportion in chronically dialyzed children. This observation was confirmed in large pediatric dialysis populations followed in registry studies. In Europe, 55 % of patients under 15 years of age on maintenance dialysis received antihypertensive drugs, and despite receiving antihypertensive therapy, 45 % of HD patients and 31 % of PD patients maintained BP levels of 10 mmHg or more above the 95th percentile [29]. The American multicenter studies reported that 53 % of HD and 40 % of PD patients (including adolescents) received antihypertensive drugs 2 years after dialysis initiation and that 68 % of dialyzed children have uncontrolled or untreated HTN at 6 months after dialysis initiation [30, 31]. The American Midwest Pediatric Nephrology Consortium Study found HTN, defined as mean casual BP ≥95th percentile, in 59 % of HD children [32]. A similar or even higher prevalence of HTN (up to 77 %) was reported by the Mid-European Pediatric Peritoneal Dialysis Study Group, by the North American Pediatric Renal Transplant Cooperative Study, by the nationwide survey in Poland, and by the recent European Society for Pediatric Nephrology registry [33-36]. These multicenter studies were based on casual BP measurements.

Using ABPM, which provides a more detailed analysis, Lingens et al. [19] found that 33 % of children and adolescents on long-term HD, and 70 % on PD, were hypertensive, as defined by standard reference data obtained from casual readings. The predialysis plasma levels of atrial natriuretic peptide (ANP), as an indicator of the volume status, correlated highly with daytime BP

in both HD and PD patients. This is in agreement with the finding of Sorof et al. who found a correlation of the ambulatory BP and interdialytic weight gain [21] but in discordance with the finding of Lingens et al. who found no correlation between these parameters [19].

An attenuated nocturnal dip in BP (non-dipping) has been observed in many adult patients receiving dialysis treatment. This reduced nocturnal dipping may lead to nocturnal HTN, which presents an unfavorable prognostic sign associated with higher cardiovascular mortality, as dialyzed patients who are non-dippers have higher incidence of LVH and cardiovascular mortality than dippers [14, 37, 38]. In the study by Lingens et al. [19], the median nocturnal decline of mean systolic and diastolic BP was 4 % and 7 % in children on HD and 9 % and 12 % in PD children, which is lower than in healthy children. In the Finnish investigation, a decreased nocturnal decline (defined as nighttime BP decrease <10 %) was noted in 40 % of children on PD [39].

The prevalence of HTN decreases after starting dialysis in HD children [36, 40]. The reason for this change of BP during time spent on dialysis is mainly better removal of fluid overload after starting HD. However, this decrease of BP is seen only in the first year after initiation of HD, and no further improvement of BP is seen beyond the first year [34, 36]. The decrease of BP is not seen in PD children [36, 40], maybe because of initially lower BP in children starting PD [36].

Etiology and Pathogenesis of Hypertension in Dialyzed Children

The two main pathogenic mechanisms contributing to HTN, before and after initiation of dialysis therapy, are hypervolemia and increased vasoconstriction. Volume overload seems to be the major pathogenic factor, first outlined by Guyton et al. [40]. Diminished glomerular filtration rate and sodium excretory capacity result in water and sodium retention, thereby increasing venous return and cardiac output. In order to prevent hyperperfusion of tissues, vasoconstriction ensues via autoregulation. This mechanism operates, however, only after some time lag. For example, it may take several weeks until volume changes in dialyzed adult patients are translated into changes in BP [41]. After the disappearance of edema, HTN may persist until strict control of hypervolemia, e.g., by extension of the dialysis time, may finally reduce BP [42]. However, hypervolemia may also occur in the absence of HTN. On the contrary, the absence of clinical signs of edema is a poor indicator of the absence of hypervolemia as intravascular hypervolemia causing HTN is often present without edema.

Increased peripheral vascular resistance caused by humoral factors inappropriate to the volume state is another explanation of HTN in dialyzed patients [43]. Activation of the renin-angiotensin aldosterone system (RAAS) was demonstrated by high plasma renin activity [44] in adult patients on HD treatment [45]. In addition, the local RAAS in the vessel walls appears to be activated in renal failure.

Furthermore, increased sympathetic activity, correlating highly with systemic BP, was documented in dialyzed adults [46]. In children, a two- to fourfold increase of plasma noradrenaline and adrenaline levels was noted during an HD session [44]. Sympathetic overactivity appears to be mediated by an afferent signal arising in the failing kidney. HD patients who had undergone bilateral nephrectomy display normalization of the sympathetic activity [47]. The finding of structural abnormalities of coronary and great arteries in experimental CKD and dialyzed patients further supports the role of elevated peripheral vascular resistance and impaired elasticity of great vessels in the pathogenesis of HTN in ESRD [48].

Another concept used to explain HTN in ESRD relates to the abnormal endothelial release of hemodynamically active compounds. Elevated plasma levels of the vasoconstrictor endothelin-1 have been reported in HD patients [49]. Endothelium-dependent vasodilatation has been reported to be impaired in uremia, reflected by reduced release or action of nitric oxide (NO) [50], possibly related to the accumulation of circulating inhibitors of NO synthetase (e.g., asymmetric

dimethyl-L-arginine, ADMA) in the plasma of adult ESRD patients as well as of children with CKD [51, 52].

Changes in the elastance properties of the large vessels (arterial stiffness) that occur in adult and pediatric ESRD patients also contribute to the development of HTN [53, 54]. HTN can be also induced by treatment with erythropoiesis-stimulating agents [55]. In contrast to the general population, elevated body mass index and obesity are not associated with HTN in dialyzed children [7]. A new pathophysiologic mechanism of HTN seems to be hyperuricemia as serum uric acid levels are associated with high BP not only in children with essential HTN but also in dialyzed children [56].

HTN is more frequent in dialyzed children with acquired CKD as primary renal disease than with congenital anomalies of the kidney and urinary tract (CAKUT) [30, 36]. This reflects mainly better removal of fluid and salt and less stimulation in RAAS in children with CAKUT than in those with glomerulonephritis even after commencing dialysis. HTN is also more prevalent in black than in white patients [34].

Finally, HTN in ESRD is related to the duration of HTN in the predialysis period and, therefore, to the original renal disease (children with CAKUT have a lower prevalence of predialysis HTN) as well as to declining residual renal function during dialysis [57]. This suggests that HTN in ESRD patients is a progressive disease related also to falling glomerular filtration rate and diuresis, the preservation of which might improve BP control and possible also modify cardiovascular risk.

Potential risk factors responsible for the development of HTN in dialyzed children are summarized in Table 23.1.

Table 23.1 Causes of hypertension in dialyzed children

Extracellular volume overload and sodium retention
Inappropriate activation of the renin-angiotensin-aldosterone system in relationship to high volume and sodium body content leading to increased vasoconstriction
Sympathetic overactivity
Impaired endothelium-dependent vasodilatation with reduced synthesis of NO and increased levels of vasoconstrictors (e.g., endothelin-1)
Hypertension derived from the failing kidney (e.g., residual renal function and increased renin secretion and sympathetic activity)
Structural changes of the arteries (arterial stiffness)
Elevated serum uric acid
Genetic factors
Iatrogenic factors (e.g., ESA, steroids, or calcineurin inhibitors for primary disease)
Secondary hyperparathyroidism
High dialysate sodium concentration
Inadequate dialysis regimen

Complications of Hypertension in Dialyzed Children

Complications from HTN are mainly produced by vascular damage and may affect different organs such as the central nervous system, kidneys, or the heart [58]. Hypertensive encephalopathy and further impairment of residual renal function may be clinical consequences of persistent HTN during dialysis therapy. In the long run, functional and structural abnormalities of the heart are the most important consequences of chronic HTN in pediatric ESRD patients. Echocardiography usually reveals normal systolic left ventricular (LV) function in the absence of severe HTN, anemia, or cardiac failure [59] and normal LV contractility [60]. However, LV diastolic dysfunction occurs in about half of adult dialysis patients and has also been demonstrated in small proportion of children [61, 62].

Four main structural abnormalities of the heart have been described in adult patients with CKD and ESRD with or without HTN [47]: (1) LV hypertrophy (LVH), (2) expansion of the nonvascular cardiac interstitium leading to endocardial fibrosis, (3) changes in the vascular architecture (thickening of intramyocardial arterioles and reduction of capillary length density), and (4) myocardial calcification. LVH is the most relevant cardiac abnormality in children with ESRD.

LVH is a strong and independent predictor of death and cardiac failure in adult dialysis patients [63]. The main risk factors for the development of LVH are systolic HTN, anemia, hyperparathyroidism, coronary artery disease, hypervolemia,

and prolonged dialysis therapy. Two forms of LVH may be distinguished [64]:

- *Concentric* (or symmetric) LVH caused by the pressure overload, leading to disproportionate overgrowth of cardiomyocytes with thickening of both interventricular septum and left ventricular posterior wall (i.e., increased left ventricular mass LVM) but normal cavity dimension (i.e., normal relative wall thickness RWT)
- *Eccentric* (or asymmetric) LVH caused mainly by volume overload, resulting primarily in dilatation of the LV chamber (i.e., increased RWT) and increased wall thickness sufficient to counterbalance the dilatation with predominant thickening of the interventricular septum and a low LV-to-volume ratio

In ESRD, both forms of LVH may be present and have also been described in dialyzed children in 70–80 % of patients [65, 66]. On the contrary, concentric remodeling (i.e., increased RWT but normal LVM) is only rarely seen in pediatric ESRD patients [66].

Although LVH is an adaptive response to chronic pressure and volume overload (allowing maintenance of systolic function), its persistence may become detrimental because it impairs diastolic compliance and reduces coronary perfusion reserve [63]. Reduced diastolic filling is closely associated with LVH and increased stiffness of the LV chamber owing to collagen accumulation [61, 62].

Many reports have described LVH in children with ESRD [59, 65, 66]. Echocardiographic examination provides reliable data but requires large experience of the investigator and cooperative patients. In addition, there is still some controversy surrounding the optimal expression of LV mass data in children with renal disease. The currently most often used expression of LV mass is the left ventricular mass index (LVMI) corrected to body size (height raised to a power of 2.7, i.e., $g/m^{2.7}$) and definition of LVH the LVMI greater than the 95th percentile for normal children and adolescents, which represents a numerical value of >40 and 45 $g/m^{2.7}$ in girls and boys older than 9 years [67, 68].

In the largest echocardiographic study reported in children with ESRD (aged <15 year), 51 % of patients on HD and 29 % on PD exhibited LVH. However, no methodological details were collected in this European ERA/EDTA pediatric registry [29]. Since then, several single centers have published detailed data on LV mass in children and adolescents with ESRD. In the study by Mitsnefes et al. [65], LV mass was increased by the start of dialysis therapy and did not change after a mean follow-up of 10 months. Risk factors for LVH were lower hemoglobin level (anemia) and longer duration of renal disease prior to start of dialysis and higher systolic BP. The degree of LVH indexed to body size (e.g., $g/m^{2.7}$) seems to be similar in pediatric and adult patients, although small children were rarely assessed. In a most recent multicenter study from the International Pediatric Peritoneal Dialysis Network, LVH was present in 48 % of children on PD with HTN, fluid overload, high body mass index, and hyperparathyroidism being the primary determinants of LVH [69]. Reduced nocturnal dipping seems to play a role in the development of LVH in dialyzed children as children with LVH displayed lower dip than children without LVH [14].

There are discrepant data on whether LVH is more prevalent in children on PD or HD. An American study has shown that children on HD have more often LVH (85 %) than children on PD (68 %, [70]). Similarly, the Finnish study has demonstrated that only 45 % of PD children had LVH and that LVH was highly correlated with the severity of HTN (pressure overload) and ANP level, a marker of volume overload [39]. On the contrary, the results from a German study showed similar LV mass index with both modes of treatment [59]. It is therefore likely that the prevalence of LVH is dependent more on the overall control of BP and volume status than on dialysis modality.

In adults on long-term HD, LVH may regress; this has been attributed to improved control of HTN, hypervolemia, or anemia [71]. Such regression of LV mass is associated with better survival [72]. In adults, LV mass may also decrease after conversion from conventional to daily nighttime HD, associated with a drop of BP [73]. In children, only very few studies investigated LV mass longitudinally during long-term dialysis.

In the Midwest Pediatric Nephrology Consortium study, no normalization of LV geometry was observed during 2 years of HD [66]. On the contrary, in a French study, a significant reduction of LVH in HD children has been reached during a median follow-up of 18 months [74], which is in agreement with adult studies showing that with adequate dialysis and control of BP and anemia, regression of LVH is possible in most patients [75]. The reduction of LVH was associated with reduction of BP, extracellular volume (represented by increased plasma protein), and improvement of anemia.

Left ventricular hypertrophy in ESRD is frequently associated with vascular lesions in the heart and great vessels, which have been extensively investigated in adult patients [48]. Two recent studies, which used new noninvasive imaging techniques (electron-beam computed tomography and high-resolution Doppler ultrasonography), revealed a high prevalence of coronary calcifications and wall thickening of the carotid arteries (coronary intima media thickness, cIMT) in former pediatric patients evaluated as young adults after long-standing dialysis and transplantation [76, 77]. A pathoanatomical study of the internal iliac arteries at the time of transplantation (i.e., after long-term dialysis) confirmed these clinical investigations that used noninvasive markers of vascular lesions such as cIMT. A recent study by Civilibal et al. on patients in the pediatric age group has demonstrated increased cIMT also in dialyzed pediatric patients, with no differences seen between children on HD and PD [78]. Diastolic BP was the only independent significant predictor of cIMT in this pediatric study showing the early evolution of cardiovascular morbidity in pediatric ESRD patients and clearly demonstrating that better management of HTN may be the priority for preventing or improving cardiovascular damage in these patients.

Increased arterial stiffness is often present in dialyzed adult and pediatric patients with ESRD and is associated with increased cardiovascular morbidity and mortality in ESRD patients independent of BP [79, 80].Therefore, decreasing arterial stiffness by improving the adequacy of dialysis or by prescribing drugs affecting the RAAS is another therapeutic target in the management of patients with ESRD.

It is well established that the high mortality of adult patients with ESRD is related to long-standing HTN. The mortality risk is increased by a large interdialytic weight gain, a high nocturnal BP, and an increased pulse pressure (difference systolic BP minus diastolic BP) [81, 82]. Long-term studies have demonstrated that adequate BP control improves the survival of adult ESRD patients [83].

Since the start of the dialysis era, there has been a remarkable decrease in early cardiovascular mortality in children and adolescents with ESRD [84, 85]. The late cardiovascular mortality has been studied only rarely in pediatric patients. According to the US Renal Data System, 1.1 and 2.0 cardiac death per 100 patient years were recorded in dialyzed pediatric ESRD patients at the age of 0–15 years in white and black subjects, respectively (normal about 0.001 in healthy children, i.e., 1,000 times less than in ESRD children), rising to 2.3 for all patients reaching the age of 20–30 years [86]. According to this study, cardiovascular mortality corresponds to approx 20–30 % of all deaths encountered in dialyzed children and young adults up to 30 years old.

It should be stressed that late fatal cardiovascular events, such as myocardial infarction and cerebrovascular accidents, are the result of both specific (uremic, nontraditional, such as volume overload, hyperphosphatemia, hyperparathyroidism, microinflammation, malnutrition, or anemia) and unspecific (traditional atherosclerotic) risk factors. However, because the cardiovascular mortality in children with ESRD is up to 1,000 times higher than in healthy children, it is likely that mainly the disease-specific – uremic – risk factors are responsible for such a tremendous increased mortality in ESRD children. A recently discovered fibroblast growth factor 23 (FGF-23) seems to be a new cardiotoxic factor associated independently of BP with LVH in dialyzed children [6, 87].

A more detailed study from the Netherlands Dutch Cohort Study analyzed the data from patients who required the initiation of renal replacement therapy from birth to 15 years of age

between 1972 and 1992. Such children had an overall mortality of 1.6 per 100 patient years, a 31-fold increase in death rate compared to normal children of similar age [85]. Patients who had spent more time on dialysis than with a functioning renal allograft had a seven times higher mortality rate. Altogether, 41 % of deaths in children on both treatments were attributed to cardiovascular causes. An interesting and clinically important finding was that patients with long-standing HTN had a threefold higher risk of death than normotensive patients. Cerebrovascular accidents on dialysis treatment were by far the most frequent cardiovascular cause encountered in this study. Therefore, the very high cardiovascular mortality risk in dialyzed children can be decreased mainly by decreasing the time spent receiving dialysis (i.e., early transplantation) and rigorous treatment of HTN.

Evaluation of Hypertensive Children on Dialysis

Every pediatric patient with ESRD should be regarded as potentially hypertensive (due to the very high prevalence of HTN including nighttime and masked HTN) and should undergo a systematic evaluation.

Casual BP recordings obtained by oscillometric devices should be regularly checked by auscultatory methods and, preferably, by ABPM as well (see "Measurement of BP" and "Definition of hypertension in ESRD," above). ABPM is especially helpful in HD patients because it allows a better recognition of intra- and postdialytic (particular nocturnal) BP changes when performed over 24 or 48 h [13]. Furthermore, ABPM allows better monitoring of antihypertensive treatment and improves patient compliance in children on all forms of renal replacement therapy (RRT). ABPM should therefore be performed regularly in all dialyzed children, at least every 6–12 months, regardless of values of casual BP.

Given the known prognostic significance of cardiovascular lesions and hypertensive end-organ damage (especially LVH) in pediatric ESRD patients, early and regularly repeated monitoring, especially of cardiac function and geometry (echocardiography), is required, even in the absence of any clinical signs of cardiovascular disease [59]. Echocardiography should be performed within 3 months of beginning dialysis and every 6–12 months thereafter [80]. There is no doubt that the collaboration of the nephrologist with an experienced pediatric cardiologist and/or radiologist considerably facilitates the cardiovascular care of children with ESRD.

The traditional markers of cardiovascular morbidity and mortality should also be checked in dialyzed children [78]. They include mainly dyslipidemia, obesity, and diabetes. Early treatment of these risk factors may improve the overall unfavorable long-term cardiovascular morbidity and mortality in pediatric ESRD patients. The nontraditional (uremia-specific) risk factors should also be carefully investigated in all dialyzed children. Volume changes should regularly and carefully be checked in hypertensive patients undergoing HD or PD. The absence of clinical signs of edema and normal pre- and postdialytic BP values are not reliable signs of normovolemia.

Therefore, additional methods to recognize increased intravascular volume should be applied in children with severe HTN or marked lability of BP. These methods include bioimpedance [88, 89], ultrasonography of the inferior vena cava [90], and determination of the ANP in plasma [39]. Although these methods are not sufficiently validated in large series of children with ESRD, their use may help in determining the individual "dry weight" at which child must carefully be maintained. It should be noted that intravascular volume is reconstituted only a few hours after the end of an HD session [8]. A new technique that can help in the assessment of child's dry weight is noninvasive monitoring of the hematocrit in HD patients (blood volume monitoring, BVM). This method has been studied also in several pediatric studies on HD patients showing better detection of volume overload and decrease of dry weight with decrease of both casual and ambulatory BP [91, 92].

The new and more sensitive methods for the detection of cardiovascular disease such as cIMT, evaluation for arterial calcification, or measurement of pulse wave velocity in pediatric dialyzed patients are still reserved for research purposes and cannot yet be recommended for routine clinical practice.

Treatment of Hypertensive Children on Dialysis

Control of volume status is the primary goal in the treatment of hypertensive children undergoing long-term HD or PD [43], as the most important cause of HTN is intravascular volume overload. Use of multiple antihypertensive drugs in the setting of fluid overload is inappropriate and very often ineffective [93]. Therefore, the appropriate initial management of HTN in a dialyzed child is gradual fluid extraction to control BP and achieve an ideal "dry weight," i.e., the weight at which most of the excess fluid has been removed [94]. In the clinical practice, in every hypertensive patient newly admitted to dialysis therapy, one should try to gradually withdraw any antihypertensive medication within 1–2 months in concert with a tolerable dietary salt and fluid restriction (which also helps to decrease thirst). During this period the true "dry weight" should become evident (see "Evaluation"). Noninvasive monitoring of hematocrit (BVM) or body composition using bioimpedance, if available, may facilitate accurate establishment of dry weight [91, 92]. In some patients (especially those without severe HTN before the initiation of dialysis), gradual normalization of BP by these measures may be obtained without antihypertensive drugs. The therapeutic results should be checked regularly by ABPM, with the aim to obtain normal daytime, as well as nighttime, BP values. The target "dry weight" should be periodically reassessed and adjusted according the child's growth and changes in muscle or fat mass.

Since compliance with the strict procedures necessitated by ESRD and dialysis is often difficult, the dialysis prescription often has to be modified to better control BP, e.g., switching to longer, more frequent (e.g., daily or 4–6 times/week), or nocturnal HD sessions or by minimizing the sodium content of food and dialysate fluid. In a randomized crossover study performed in adult patients, daily HD sessions (6 times 2 h/week over 6 months) were able to significantly reduce extracellular water, mean 24-h BP, and LV mass compared with conventional HD (3 times 4 h/week), and antihypertensive medications were able to be stopped or reduced in most subjects [95]. A similar study has been performed recently in children in which after 16 weeks of frequent HD (6 times/week), the patients exhibited progressive reduction in casual predialysis BP, discontinuation of antihypertensive medications, and decreased BP load by ABPM [96]. Similar results were obtained in adult patients switched from conventional to nocturnal dialysis [73]. In other studies, reduction of predialysis BP was obtained by gradually lowering the dialysate sodium content during HD sessions [97]. However, fluid removal is sometimes limited by hypotensive episodes occurring during the HD procedure, related either to exaggerated ultrafiltration or to concurrent use of high doses of diuretics or antihypertensive drugs. Therefore, antihypertensive drugs should be, whenever possible, withdrawn before attempts at reaching adequate fluid removal during HD to minimize hypotensive episodes and to be able to reach the true dry weight.

Another approach to improving BP control in dialyzed children and to reduce dialysis-associated events is to follow a standard noninvasive monitoring (NIMV) of hematocrit algorithm. In a recent 6-month study using NIVM of hematocrit on 20 pediatric HD patients, there was a decrease in postdialytic casual BP, daytime ambulatory BP, number of antihypertensive medications prescribed, and rate of intradialytic events related to ultrafiltration [91].

Whether conversion from HD to PD has any persistent favorable effect on the BP status is controversial. On the other hand, prolonged conservation of residual urine volume during HD or PD treatment generally allows for dialysis with less aggressive ultrafiltration. From this point of

view, HD leads to faster loss of residual diuresis than PD and can therefore be potentially associated with increased risk of HTN during long-term HD treatment when residual urine output is decreasing [98]. Above all, application of all criteria for adequate dialysis is important in both hypertensive and normotensive pediatric dialysis patients.

Another important issue in the treatment of HTN in dialyzed patients is sodium restriction. A salt (NaCl)-restricted diet (<6 g/day) has been shown to reduce peripheral vascular resistance and BP in adult patients [99]. However, adherence to sodium-restricted diets is low, especially if it has to be combined with fluid restriction. No pediatric data are available on the effect of salt-restricted diet on BP during dialysis.

A dialysis regimen with low-sodium dialysate fluid concentration (135–136 mmol/l) can reduce BP in adult patients [100]. Similar effects can also be expected in pediatric patients; however, no studies have been performed in children. The use of diuretics can decrease the sodium content in the body and reduce BP in dialysis patients, at least in those children with residual urine output.

It is generally agreed that antihypertensive drugs should be used in dialyzed children only if BP remains elevated, despite seemingly adequate volume and sodium control – i.e., after reaching true dry weight. Since no controlled studies have been performed in this group of patients, the optimal drug therapy remains empiric, based on investigations performed in other hypertensive populations. Angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers (CCBs) appear to be the most frequently used antihypertensive agents used in dialyzed children. In the EDTA study, they were given to 62 % and 56 % of children on HD and PD, respectively, followed by beta-blockers (35 % and 44 %, respectively), alone or in combination with other drugs [29]. In the recent nationwide survey in Poland, ACE inhibitors and CCBs were given to 50 % and 46 % of dialyzed children, respectively [35]. The antihypertensive drugs mentioned are usually well tolerated, but the prescribing physician must note their multiple side effects, contraindications, and dose modifications in renal failure most carefully (see Chap. 28).

There are emerging data that suggest that ACE inhibitors and angiotensin receptor blockers may have a greater effect on decreasing cardiovascular morbidity and mortality in dialyzed patients than other groups of antihypertensive drugs [101] and are recognized as first-line therapy in the pharmacologic management of HTN in adult HD patients [102]. However, some trials showed lower final BP in groups of patients with ACE inhibitors or ARBs than in groups of patients with other drugs, and it is therefore not yet clear whether ACE inhibitors and ARBs have cardioprotective effects beyond their BP-lowering effects in dialyzed patients. CCBs have also been shown to reduce LV mass and may be used even in the presence of volume overload. The less frequent application of beta-blocking agents in children with ESRD may be related to their side effects (bradycardia, hyperlipidemia, etc.), but according to a recent study in adults, they may contribute to improved survival [82]. In many cases, the hypotensive agents, as well as diuretics, have to be combined in order to obtain adequate BP control. In the Polish nationwide survey, 66 % of treated children received two or more antihypertensive drugs [35]. Despite all these efforts, the control of HTN in dialyzed children is still rather poor. Tkaczyk et al. showed that the effectiveness of antihypertensive treatment in pediatric patients on HD and PD was only 58 % [35], and the recent ESPN/ERA-EDTA Registry study showed uncontrolled HTN in 64 % of treated HD and in 55 % of PD children [36].

Drug-resistant HTN is rare and usually the result of inadequate ultrafiltration (fluid overload) but may also be due to a paradoxical (heightened) response of the RAAS to ultrafiltration. Noncompliance with the recommended fluid and dietary measures and pharmacological treatment can be other reasons for poor BP control in dialyzed children. In compliant children who remain hypertensive despite achievement of true dry weight and are oligo-anuric, bilateral native kidney nephrectomy should be considered [47]. The treatment algorithm for dialyzed children is summarized in Fig. 23.1.

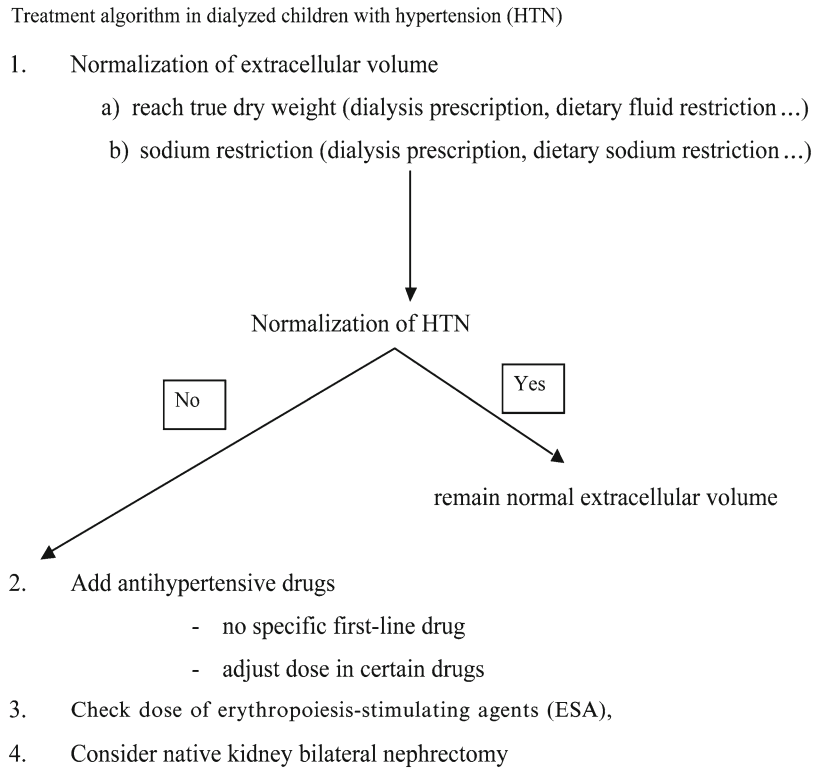

Fig. 23.1 Treatment algorithm in dialyzed children with hypertension

Hypertension in Children After Renal Transplantation

Introduction

Hypertension is a common and serious complication in patients after renal transplantation [103, 104]. It is an important risk factor for cardiovascular morbidity and mortality in transplanted patients [105]. Furthermore**,** it is a strong risk factor for impaired graft survival in adult and pediatric patients [106, 107].

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 in 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 [108]. The main reasons are the ability of ABPM to reveal white-coat or masked HTN and to measure BP during nighttime. Furthermore, ABPM is superior to casual BP in regard to better correlation with target-organ damage such as left ventricular hypertrophy [109] in children with after transplantation. Finally, the results of ABPM are more closely related to renal function in transplanted patients than the results of casual BP [110]. Therefore, regular use of ABPM is recommended in all patients after renal transplantation regardless of the values of casual BP [111, 112]. 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 [113, 114]. 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) has been revealed in 30–72 % of transplanted children [113, 114]. Adult transplant patients who are non-dippers have greater left ventricular mass than dippers [115]. 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 [114]. The reproducibility of dipping status in transplanted children is low [116]; 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.

Home BP self-measurement is also an important method for the measurement of BP. It is increasingly used as a valuable supplement to casual BP and also ABPM in children with CKD, those on renal replacement therapy or following transplantation [22]. It is especially recommended in children receiving antihypertensive medication to improve control of HTN and to support compliance with the medication.

Definition and Prevalence of Hypertension in Transplanted Children

The same definition is used for transplanted children as for otherwise healthy children or children on dialysis. The prevalence of HTN in children after renal transplantation ranges considerably between 58 % and 89 % [36, 103, 104, 113, 114, 117]. 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 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 [118].

Moreover, children should be defined as hypertensive on the basis of two criteria – the use of antihypertensive drugs and current BP level and the control of HTN should also be assessed according to these criteria. 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 [108, 119]. Therefore, using only one category of HTN (regardless of the therapeutic control of HTN) or antihypertensive drugs as the only criterion for the 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.

Etiology and Pathogenesis of Hypertension in Transplanted Children

The etiology of posttransplant HTN is multifactorial [103, 104, 120, 121]. The main causes are summarized in Table 23.2.

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 [114, 120]. Children receiving kidneys from deceased donors are more frequently hypertensive than children receiving grafts from living donors [104, 117, 120]. 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

Table 23.2 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 posttransplant weight gain
Genetic factors (primary – essential hypertension, genes of RAAS)
Recurrent or de novo renal disease (IgA nephropathy, focal segmental glomerulosclerosis)
Others (e.g., polycythemia, pyelonephritis, ureteric obstruction, lymphocele)

episodes of acute rejection, the only independent determinant of graft survival in children after living donor transplantation [122].

Steroids are a well-known risk factor for posttransplant HTN. Several factors such as sodium retention or increase in cardiac output and renal vascular resistance induce steroid-related HTN. Elimination of steroids in stable patients showed reduction of BP in adult as well as in pediatric patients [123, 124], and children treated under a steroid avoidance immunosuppressive protocol showed improvement in HTN [125]. In a cross-sectional study the patients on alternate-dose steroid treatment showed significantly lower prevalence of HTN than children on daily steroid medication [113], and other studies showed that conversion from daily to alternate-dose steroid therapy significantly reduces BP [126]. Therefore, adoption of steroid-sparing or steroid-free immunosuppression regimens can be considered a treatment strategy for improving the 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 [120]. Gordjani et al. [120] 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 [127]. 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 the control of HTN in transplanted children [128].

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 decline of graft function. In adults, impaired graft function is associated with elevated BP and increased risk of HTN [110, 119, 129]. 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 [108]. However, hypertensive children had reduced allograft function (glomerular filtration rate GFR <50 ml/min/1.73 m2) more frequently than normotensive patients, whereas children with normal BP more frequently had normal graft function (GFR >75 ml/min/1.73 m2).

Current body weight or change of body weight is a well-known and potent determinant of BP level in adults and children [130], and most children gain weight after renal transplantation [131]. Therefore, control of body weight should be recommended in all children after renal transplantation to improve BP control.

Stenosis of the graft artery has become a rare cause of HTN with current surgical technique using aortic patches [132]. 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 [133].

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. [106] 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 [105, 108]. Hypertensive pediatric transplant recipients have worse long-term graft survival than normotensive recipients (Fig. 23.2). 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 [104]. Increased BP is therefore clearly 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. [108] showing that HTN is associated with allograft failure in children with normal graft function but not in children with severely impaired graft function suggest that HTN is not only a marker of graft dysfunction but also a direct cause of renal graft damage (Fig. 23.2).

Similar to the general population, HTN is also associated with increased cardiovascular morbidity in transplanted patients. Left ventricular hypertrophy (LVH) is a frequent type of cardiac end-organ damage in hypertensive children after renal transplantation, occurring in 50–82 % of children [113, 114]. Matteucci et al. [134] found a correlation between left ventricular mass index (LVMI) and mean 24-h systolic BP, but Morgan et al. [113] could not demonstrate any relationship between LVMI and ambulatory BP data. However, in a recent study by Kitzmueller et al., there was a correlation between LVMI and

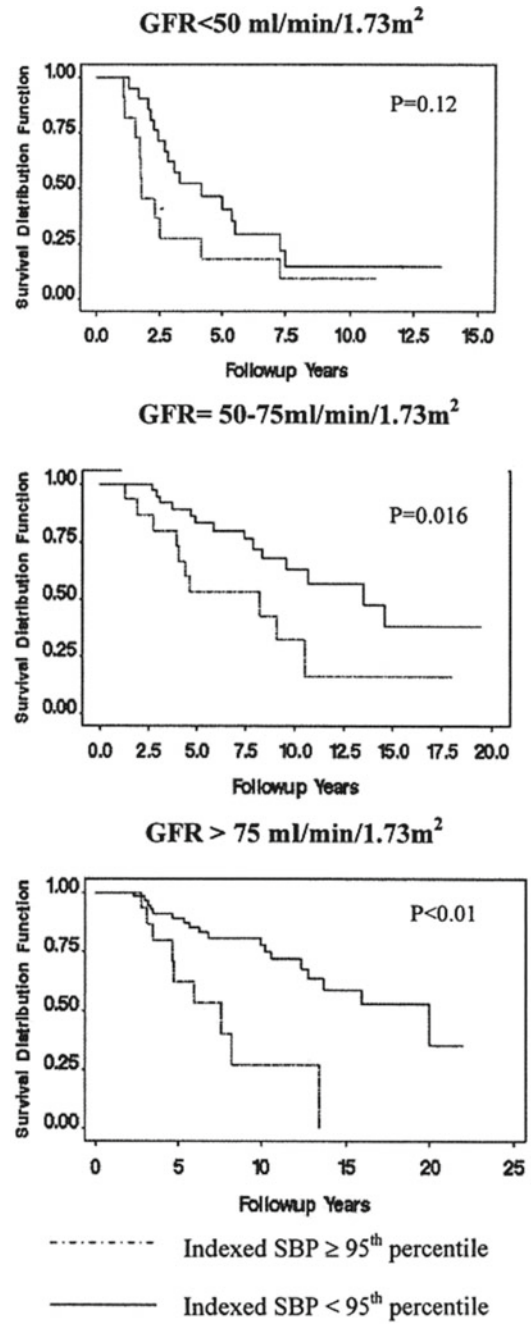

Fig. 23.2 Renal allograft survival by 1-year indexed systolic BP and 1-year graft function (Reprinted from Mitsnefes et al., [108], Fig. 2)

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 [135]. 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 [54, 136-138].

Hypertension is also a risk factor for increased cardiovascular mortality seen in transplanted adult patients [139]. Similar studies in children are rare. The Dutch Cohort Study has demonstrated that HTN is one of the most powerful risk factors for cardiovascular morbidity and mortality in children after renal transplantation [85]. 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 the high prevalence of nocturnal or masked HTN. This recommendation has been firstly used by the European Society of Hypertension in its pediatric recommendations [111] and has recently been recommended also by other experts [112]. ABPM should be performed at least once a year and about 6 months after the change of antihypertensive medication to check for the control of HTN with changed antihypertensive therapy.

The diagnostic evaluation of HTN in transplanted children should consider the multiple etiologies of posttransplant HTN (Table 23.2). Echocardiography should be assessed at least once a year to determine the presence or absence of hypertensive target-organ damage on the heart [140]. As in dialysis patients, 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 similarly to HTN in children with CKD. 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 (CCBs) 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 [141, 142].

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 to 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 [143, 144]. Moreover, they can reduce proteinuria which in addition to HTN is another treatable risk factor for impaired graft survival [145]. Furthermore, ACE inhibitors and ARBs can slow the progression of chronic native kidney diseases mainly by long-term reduction of intraglomerular pressure. 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 on 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 [144, 146]. However, the results from the CTS published recently did not show any improvement of patient or graft survival in patients treated with ACE inhibitors [147]. 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 [148, 149]; however, they seem to have similar risks and benefits as ACE inhibitors. Beta-blockers are also effective drugs in transplanted patients [150]. 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 hyperlipidemia, hyperuricemia, or hyperglycemia. 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 [141]. In most pediatric renal transplantation centers, the most commonly used antihypertensive drugs are CCB, which are given to 38–65 % of transplanted children [113, 114, 118]. 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, 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).

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 [151]. 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 [152]. However, it is not known whether these results can be extrapolated to transplanted children as no similar study has been performed in kidney graft 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 [111]. 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 [153, 154].

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 [32, 114, 117]. The prevalence of

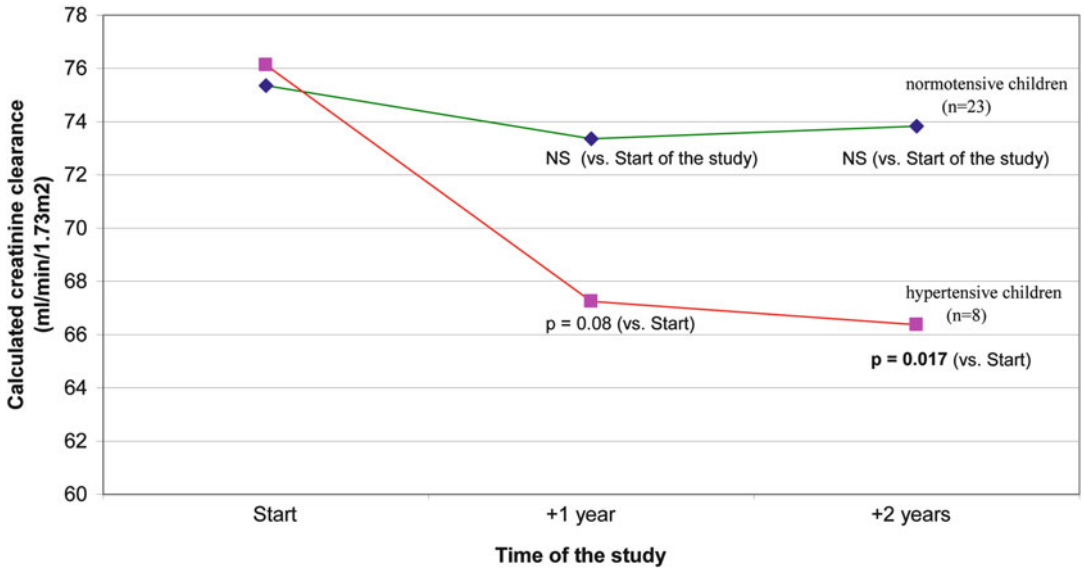

Fig. 23.3 Graft function in children being normotensive and hypertensive at 2 years during a 2-year interventional study (Reprinted from Seeman et al., [153], Fig. 3)

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 [32, 113, 114, 117]. 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 the 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 can play an important role in the control of HTN, particularly in adolescent patients. Therefore, adherence not only to the recommended immunosuppressives but also to antihypertensive drugs should be checked during every outpatient visit.

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 [155]. Three recent studies have demonstrated promising result on this issue also 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. 23.3) [154]. 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 the decrease of systolic and diastolic BP index [156]. 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 % [157]. These most 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.

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Vascular Hypertension in Children

24

Kjell Tullus

Abstract

High blood pressure in children is in a significant proportion caused by some vascular abnormality. 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. The vascular abnormalities are important to diagnose as in most cases they are amenable to surgery or angioplasty.

Keywords

Renovascular hypertension • Renal artery stenosis • Mid-aortic syndrome • Angiography • Renal vein renins • Angioplasty • Stenting • Coarctation aorta

The causes of vascular hypertension include narrowing of the renal arteries, narrowing of the abdominal part of the aorta, mid-aortic syndrome, or narrowing of the aortic arch, coarctation of the aorta [1, 2]. I will here discuss these different entities.

Renovascular Disease

Renovascular disease (RVD) is a relatively uncommon but important cause of hypertension in children as it is, in many cases, possible to treat with angioplasty or surgery; for a more extensive review, please see [3]. 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 [4]. Both renal arteries are affected in between 53 % and 78 % of cases, and intrarenal small artery disease is found in a third of the children [5, 6]. A large percentage (20–48 %) have associated mid-aortic syndrome (MAS) [7, 8], 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 %.

The mechanisms for the hypertension in renovascular disease are increased secretion of renin due to hypoperfusion, with consequent retention

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Table 24.1 Causes of renovascular hypertension in children [3, 9]

Fibromuscular dysplasia
Syndromic
Neurofibromatosis type 1 (NF-1)
William's syndrome
Tuberous sclerosis
Marfan's syndrome
Other syndromes
Vasculitis
Takayasu's disease
Polyarteritis nodosa
Kawasaki disease
Other systemic vasculitides
Extrinsic compression
Wilms' tumor
Pheochromocytoma
Lymphoma
Other tumors
Other causes
Post radiation
Post umbilical catheters
Trauma
Rubella syndrome
Transplant renal artery stenosis

of sodium, leading to volume expansion. Increased sympathetic nerve activity can also play a role.

Etiology

There are many causes for RVD in children, and they are quite different from those in adults, where atherosclerotic disease is the predominant diagnosis (Table 24.1) [3, 9]. Certain syndromes, in particular neurofibromatosis type 1 and William's syndrome, are overrepresented among children with RVD even if most children with these syndromes do not show RVD [10–12]. Acquired conditions like tumors, radiation, and trauma can also cause significant RVD.

The two main diagnosis causing RVD are fibromuscular dysplasia (FMD) and Takayasu arteritis (TA). The occurrence of these diagnoses varies quite markedly in different parts of the world [9]. In many centers, FMD is most

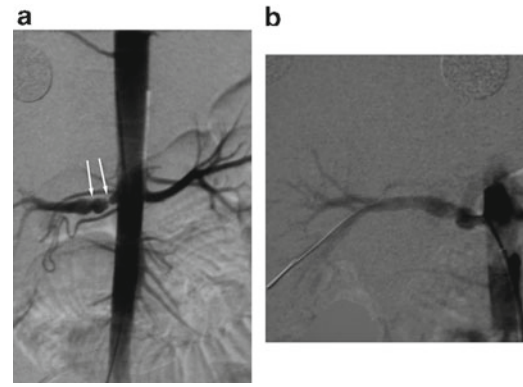

Fig. 24.1 (**a**) Typical beaded appearance of a renal artery with severe stenosis, (**b**) after treatment with angioplasty

common [13, 14] while in other parts of the world, e.g., India, TA is the most common diagnosis [15, 16]. The reason for these regional differences 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.

FMD is a disease affecting one or several layers of the blood vessel wall without any known cause. It is mostly a diagnosis of exclusion as the typical pattern on angiography with so-called beading (Fig. 24.1a) often is not present. It is also uncommon to have pathological confirmation of the diagnosis as only a minority of children will have surgery. TA is an autoimmune condition affecting large blood vessels.

The differential diagnosis between FMD and TA is, however, in many cases not as straightforward as one might think. The diagnostic criteria overlap to a large extent and involvement of similar blood vessels is often seen [9]. Many cases of TA are diagnosed in the silent phase, and no signs of inflammation can be detected, either by clinical symptoms or by laboratory testing. 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 [^{18}F]

fluorodeoxyglucose positron emission tomography (FDG PET) scan can also be helpful in some cases to establish the presence of inflammation in the blood vessel wall.

The vascular disease in many children with FMD is progressive. The number of blood vessels, renal and extra renal, 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.

Presentation

Children with RVH often present with very high BP; it is not uncommon with 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 [17, 18]. At the other side of the spectrum, some children present with very severe potentially life-threatening cerebral or cardiac symptoms such as stroke and heart failure [6, 17, 19, 20].

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.

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. 24.1) [4, 21]. The sensitivity and specificity of other imaging methods is presented in Table 24.2. Angiography is, however, invasive and general anesthesia is needed in most cases. Other less-invasive investigations can therefore be used to help to define the group of children that need to undergo DSA. Table 24.3 list situations where we recommend performing a 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.

Table 24.2 Diagnostic accuracy of ultrasound, pre- and post-captopril isotope studies, CTA and MRA

Technique	Sensitivity	Specificity
US	73–85 %	71–92 %
Captopril renography	52–93 %	63–92 %
CTA	64–94 %	62–97 %
MRA	64–93 %	72–97 %

Table 24.3 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 ≥ 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

Renal Doppler ultrasound may in some cases be very helpful in detecting RVD, but in many cases, it is unable to detect the renal artery stenosis (Fig. 24.2) [22–24]. The resistive index has been used to measure blood flow in kidneys, but the sensitivity is too low for it to definitively rule out a need for angiography [25]. This procedure is highly operator dependent, and even in the best hands at the present time, only has a sensitivity of 73–85 % and a specificity of 71–92 % [26].

Pre- and post-captopril renal scintigraphy has been widely used to screen for RVD. This elegant

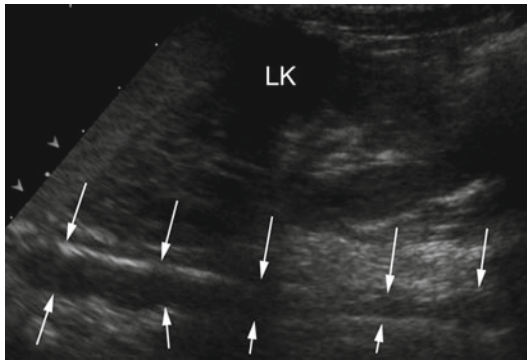

Fig. 24.2 Narrowed aorta in mid-aortic syndrome clearly shown on ultrasound

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) [27]. This can is some cases can this 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 [23, 28–32].

Newer imaging modalities such as computed tomography angiography (CTA) and magnetic resonance angiography (MRA) can be helpful in detecting and monitoring vascular lesions (Fig. 24.3). 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 [3, 23, 33, 34]. 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 [35]. As children have even smaller blood vessels, this might be a bigger problem in the younger population. We do experience that CTA and MRA can both over- and under-diagnose 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 [36–38]. 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 helpful only in a very small group of children. We do instead use renal vein renin levels to try to define which part of the kidney(s) that produces increased levels and with that help us in deciding which, of often several, artery stenoses that should be given priority in the treatment.

Treatment

The treatment of children with RVD should be managed by a multidisciplinary team and should be based on a combination of antihypertensive drugs, angioplasty, 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 [39]. 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.

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 TNFα blockers [9]. Frequently a combination of immunosuppressive therapy and endovascular procedures will be needed to successfully treat the hypertension in patients with TA [40].

Angioplasty

It is not uncommon that children with RVD are treated with 6–7 antihypertensive drugs still without effective control of their blood pressure.

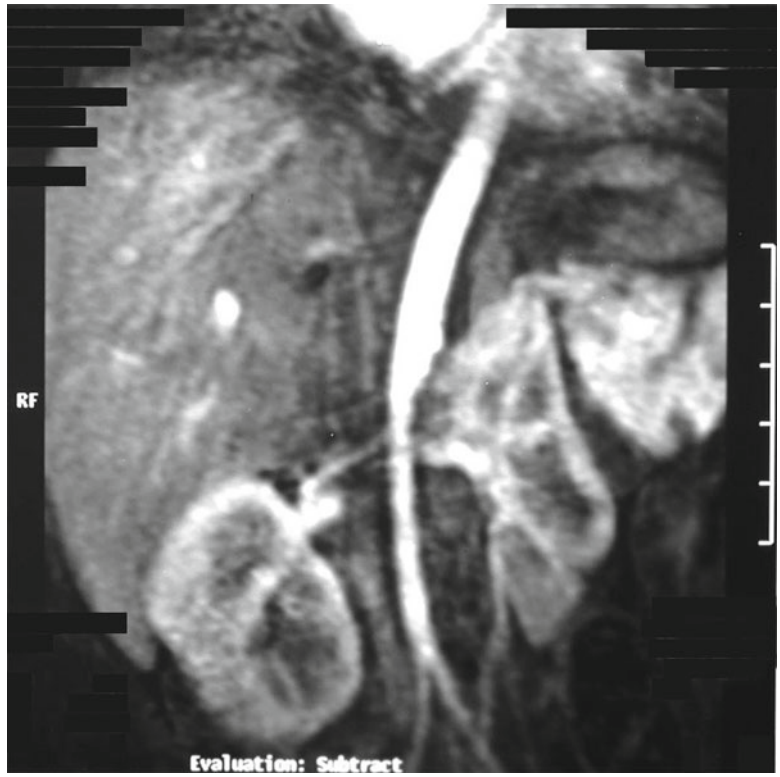

Fig. 24.3 MRA picture showing a narrowed aorta and a suspicion of left-sided renal artery stenosis

Angioplasty is in these cases the most commonly used treatment, and it can, with modern technology, cure or improve the blood pressure in at least 50 % of children [17, 41, 42]. The artery can, in some children, after successful angioplasty, recoil and cause a residual stenosis. Placement of a stent will, in such cases, help to keep the artery open [17, 43–45] (Fig. 24.4). 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 [46].

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 a widespread vascular disease that even successful treatment of some stenotic arteries is not enough.

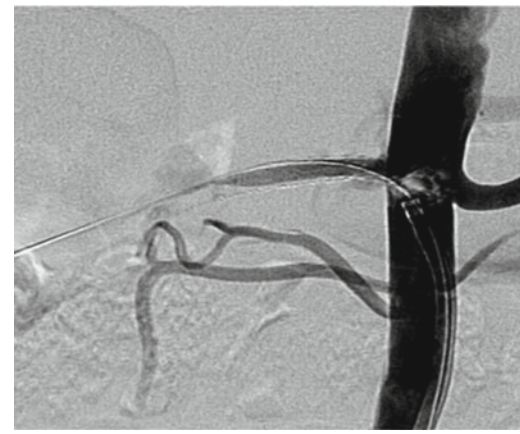

Fig. 24.4 Renal artery stented after angioplasty

The remaining disease continues to drive the high blood pressure [17]. This can be vascular disease in the other kidney or intrarenal vascular disease that is not amenable to treatment.

Children with severe MAS can also benefit from angioplasty. We have seen cases diagnosed

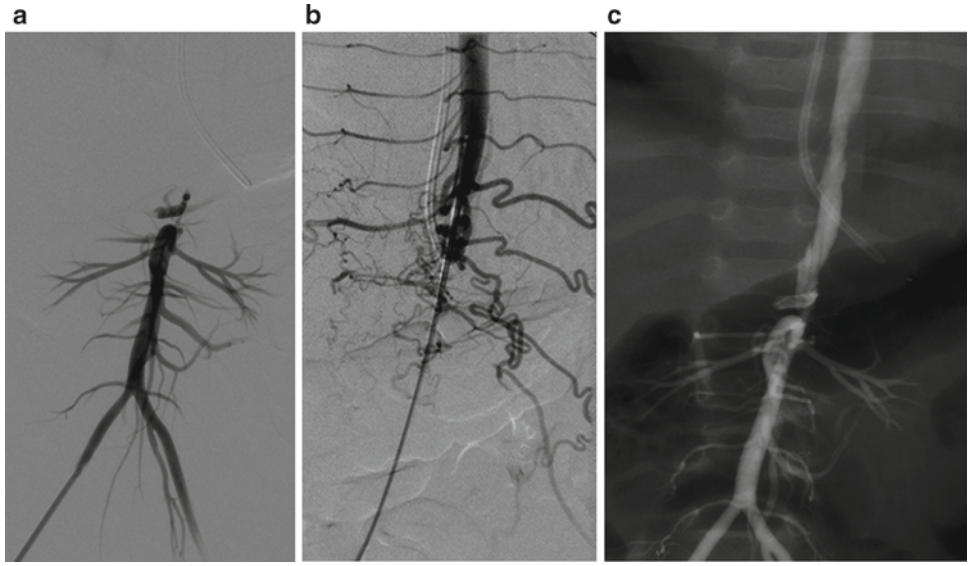

Fig. 24.5 (**a**) Mid-aortic syndrome with severely narrowed aorta, no contrast passing by the narrowed part, contrast injected from below. (**b**) Contrast injected from above, note collaterals, (**c**) after angioplasty showing an open but not normal looking aorta that functions very well

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. 24.5) [47].

Some children with stenotic vascular lesions that are not amenable to angioplasty can be treated with ethanol ablation of a part of a kidney [38, 48]. 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. There are many different surgical revascularization procedures. It can be performed using autologous or synthetic grafts [18, 49–51]. The autologous grafts can be the splenic or the gastro-duodenal 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. 24.6). 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. 24.6).

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 nonfunctioning kidney [51, 52]. A word of caution is, however, warranted; we do sometimes see kidneys that on a pretreatment DMSA scan show less than 10 % function that after successful angioplasty or revascularization surgery recover function even up to 50 % relative function (Fig. 24.7) [53]. 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 use of 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 90 % of these children [18, 51].

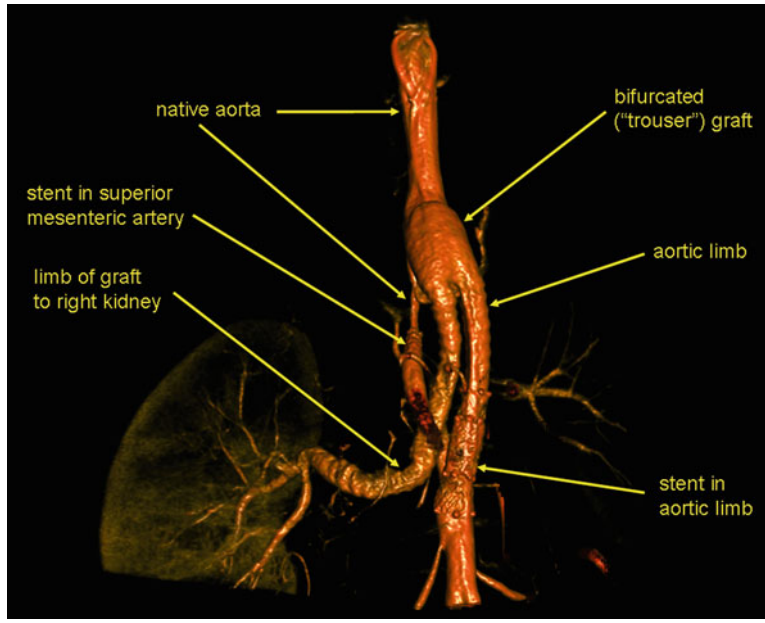

Fig. 24.6 A so-called trouser graft from upper aorta linking on to lower aorta and right renal artery

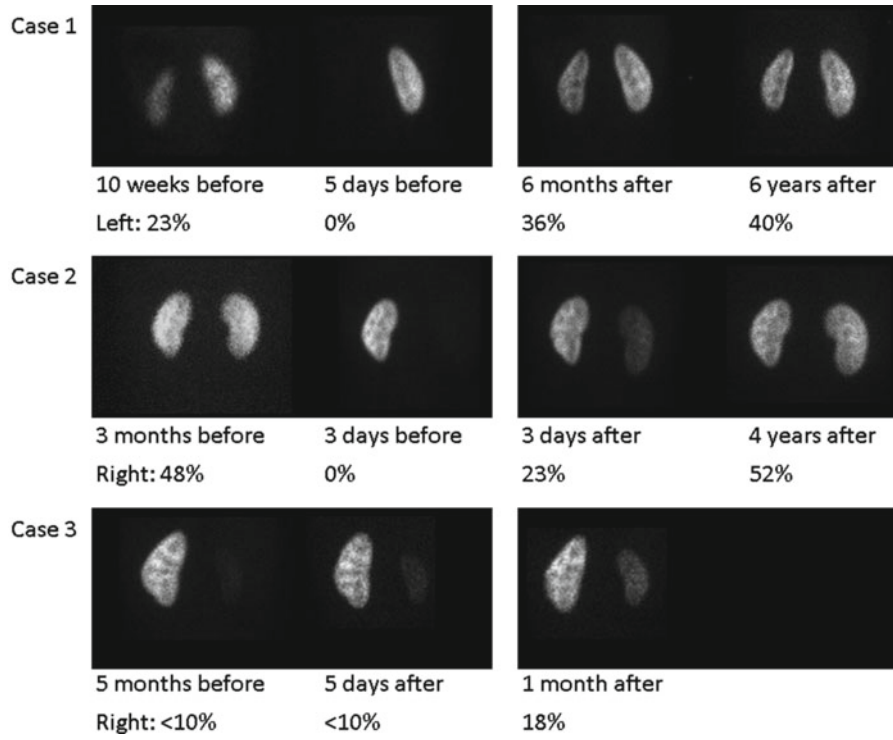

Fig. 24.7 Recovery of kidney function as measured by DMSA after revascularization of kidney with severely stenosed renal artery

Coarctation of the Aorta

Coarctation of the aorta (CoA) accounts for a few percent 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 [54, 55]. CoA is mostly diagnosed in newborn children or infants but may be detected later in life. 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 [55–58].

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 [54].

Most of these children display signs of left ventricular hypertrophy. The optimal treatment has with time become controversial [59]. 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 [60]. This is, however, in particular in smaller children quite controversial [55].

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 post surgery. About 65 % of children will, however, experience a paradoxical rise of their blood pressure in the postoperative period. This can be successfully treated with a beta-blocker like propranolol or esmolol [61].

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 had their surgical repair at a mean age of 0.2 years [62]. The chance for hypertension was higher in children treated at an age of more than 1 year compared to children who were treated earlier [57, 63]. This late reoccurrence of hypertension is only in a few children caused by reappearance of the stenosis. Reduced aortic compliance and a blunted baroreceptor reflex response are other likely mechanisms [64]. Beta-blockade seems to be the preferred treatment of this hypertension [65, 66].

There are also other long-term complications after surgery for CoA; in a Danish study 35 out of 156 patients needed cardiovascular reinterventions, 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 reinterventions. [67]

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Endocrine Hypertension

25

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 syndrome (excessive glucocorticoid exposure) due to iatrogenic etiologies, to pituitary or adrenal adenomas, or 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 condition.

Keywords

ACTH • Adrenal • Aldosterone • Catecholamines • Congenital adrenal hyperplasia • Cortisol • Cushing syndrome • Graves disease • Thyrotoxicosis • Thyroxine

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Hypertension may be caused by abnormal synthesis of, or response to, various hormones. The proportion of pediatric hypertension cases resulting 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. 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. 25.1). 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 [1]. 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 the peripheral vascular resistance, decreases the diastolic pressure. The hyperglycemic and hypermetabolic effects of norepinephrine are much less pronounced than are those of epinephrine.

Pheochromocytomas are catecholamine-secreting tumors arising from chromaffin cells. The most common site of origin (approximately 90 %) is the adrenal medulla; however, tumors may develop anywhere along the abdominal

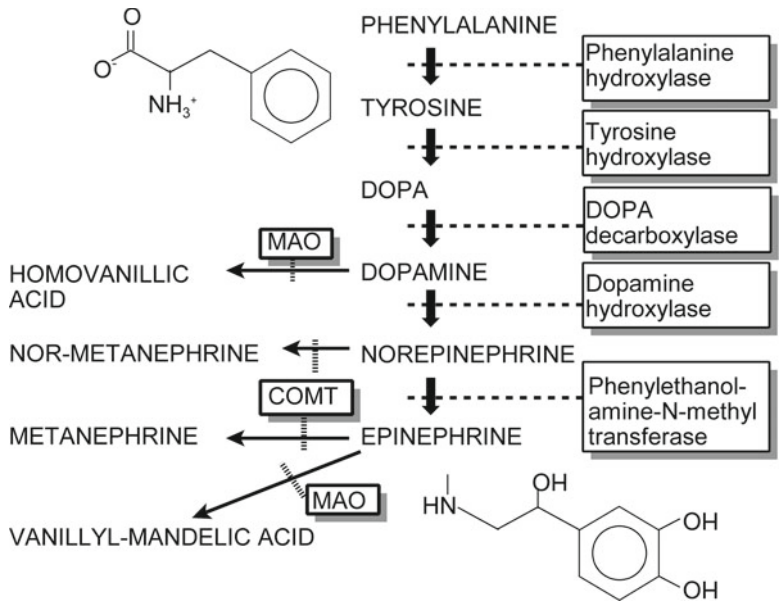

Fig. 25.1 Biosynthesis (*right side of figure*) and metabolism (*left side of figure*) of the catecholamines norepinephrine and epinephrine. COMT, catechol-*O*-methyltransferase; MAO monoamine oxidase. Planar structures of phenylalanine and epinephrine are shown at the top and bottom of the figure, respectively

sympathetic chain and are likely to be located near the aorta at the level of the inferior mesenteric artery or at its bifurcation. They also appear in the peri-adrenal 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 [2].

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 pheochromocytomas and also paragangliomas, particularly at sites in the head and neck.

Somatic mutations of many of these genes, particularly *VHL*, have been found in some sporadic cases of pheochromocytoma [3–6].

Clinical manifestations. Pheochromocytomas detected by surveillance of patients who are known carriers of mutations in tumor-suppressor genes may be asymptomatic [6, 7]. 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. 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 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. 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 μg/24 h. Urinary excretion of metanephrines (particularly normetanephrine) is also increased [6, 8]. 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.

Elevated levels of free catecholamines and metanephrines can also be 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 [9]. 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 [10, 11].

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. ^{131}I-metaiodobenzylguanidine (MIBG) is taken up by chromaffin tissue anywhere in the body and is useful for localizing small tumors [12, 13]. 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 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 [14].

Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma 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 [10, 11]. 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 α- and β-adrenergic blockade are required [6, 15]. 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, the only accurate indicators of malignancy are the presence of metastatic disease, local invasiveness that precludes complete resection, or both [16]. Approximately 10 % of all adrenal pheochromocytomas are malignant, but such tumors are rare in childhood. Pediatric malignant pheochromocytomas occur more frequently in extra-adrenal sites and are often associated with mutations in the SDHB gene encoding a subunit of succinate dehydrogenase [4, 17].

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-fourth 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. 25.2) [18]. 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 deoxycorticosterone. Deoxycorticosterone then reenters mitochondria and is converted to

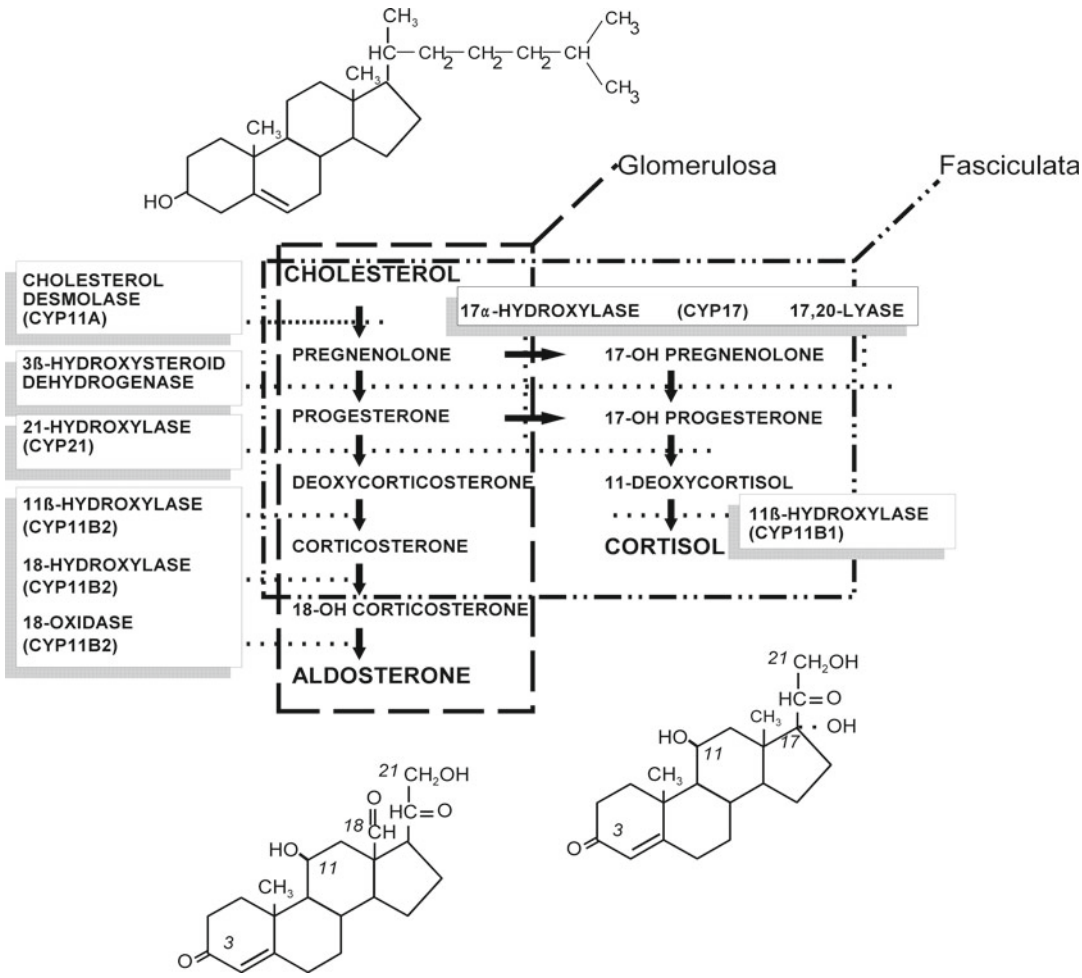

Fig. 25.2 Adrenal steroid biosynthesis. Reactions occurring in the zonae glomerulosa and fasciculata are enclosed by labeled dotted lines; several reactions take place in both zones. Many of the involved enzymes are cytochromes P450 (CYP). CYP11B2 mediates successive 11β-hydroxylase, 18-hydroxylase, 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

aldosterone by aldosterone synthase (P450aldo, CYP11B2), a P450 enzyme which carries out three successive oxidations: 11β-hydroxylation, 18-hydroxylation, and further oxidation of the 18-methyl carbon to an aldehyde [19].

In the endoplasmic reticulum of the zona fasciculata, pregnenolone is converted by 17α-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 11-deoxycortisol reenters mitochondria and is converted to cortisol by steroid 11β-hydroxylase (P450c11, CYP11B1). This enzyme is closely related to aldosterone synthase but has low 18-hydroxylase and nonexistent 18-oxidase activity [19]. Thus, under normal circumstances, the zona fasciculata cannot synthesize aldosterone.

Regulation of cortisol secretion. Glucocorticoid secretion is regulated mainly by adrenocorticotropic 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) [20]. Cyclic AMP has short-term (minutes to hours) effects on cholesterol transport into mitochondria by increasing expression of steroidogenesis acute regulatory (StAR) protein [21]. 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 α_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. Angiotensin II and III are potent stimulators of aldosterone secretion; angiotensin II is a more potent vasopressor agent. Angiotensin II and III occupy a G protein–coupled receptor activating phospholipase C [22]. The latter protein hydrolyzes phosphatidylinositol bisphosphate to produce inositol triphosphate and diacylglycerol, which raise intracellular calcium levels and activate protein kinase C and calmodulin-activated (CaM) kinases [23]. 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 [24, 25].

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, 11β-hydroxysteroid dehydrogenase type 1 (HSD11B1) converts cortisone, which is not a ligand for the glucocorticoid receptor, to cortisol, which is an active glucocorticoid [26]. This increases local glucocorticoid concentrations in several tissues, especially the liver. Conversely, 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2) oxidizes cortisol to cortisone, particularly in the kidney, preventing mineralocorticoid receptors from being occupied by high levels of cortisol [27, 28] (see Chap. 6, 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 [1]. Moreover, they have a permissive effect on the actions of epinephrine and norepinephrine on both the heart and the blood

vessels [29]. 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 11β-hydroxysteroid dehydrogenase is saturated by excessive levels of glucocorticoids.

Actions of mineralocorticoids. The most important mineralocorticoids are aldosterone and, to a lesser degree, 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 [30]. 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 [31].

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 [30]. 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 Na^+, 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 [32] (see also Chap. 6).

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 11β-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 glycyrrhetinic acid) or licorice-flavored chewing tobacco; the genetic condition is termed apparent mineralocorticoid excess syndrome [27, 28] (see Chap. 6).

Hypertensive Forms of Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia due to 11β-hydroxylase deficiency. Deficiency of 11β-hydroxylase is caused by mutations in the *CYP11B1* gene located on chromosome 8q24 [33, 34]. Its incidence has been estimated to be 1/250,000 to 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

[35]. 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^2/d. Hypertension often resolves with glucocorticoid treatment but may require additional therapy 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 remediable) aldosteronism.

Aldosterone-secreting adenomas are usually unilateral and have been reported in children as young as 3 1/2 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. 6) 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 by the RAAS. The disorder is caused by unequal meiotic crossing over events between the adjacent *CYP11B1* (11β-hydroxylase) and *CYP11B2* (aldosterone synthase) genes, which produces a third chimeric gene with regulatory sequences of *CYP11B1* juxtaposed with coding sequences of *CYP11B2* [36, 37]. 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. 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. Mutations in the KCNJ5 gene on chromosome 11q24 have been identified in several kindreds; these mutations (G151R and G151E) altered channel selectivity, producing increased Na^+ conductance and membrane depolarization, which increases aldosterone production and proliferation of adrenal glomerulosa cells [38]. Moreover, such mutations have been identified in a subset of sporadic aldosterone-producing adenomas [39].

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 [40]. However, both renin and aldosterone levels may vary by time of day, posture, and sodium intake, making it difficult to establish consistent reference ranges. Therefore, a consistent sampling protocol should be used, for example, midmorning 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, β-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 hyperaldosteronism, 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. 6).

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 [41, 42].

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 antimineralocorticoid that is safe and effective in children with hypertension, but has not been examined specifically in those with aldosteronism [43]. 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 [41, 42, 44].

Glucocorticoid-suppressible aldosteronism is managed by daily administration of a glucocorticoid, usually dexamethasone, 25 μg/kg/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 Syndrome

Pathophysiology. Cushing 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 (adrenocorticotropic hormone

[ACTH]) by the pituitary (Cushing disease) or by a tumor.

The most common cause of Cushing syndrome is prolonged exogenous administration of glucocorticoid hormones, especially at the high doses used to treat lymphoproliferative disorders. Endogenous Cushing syndrome is most often caused in infants 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 syndrome in children older than 7 years of age is Cushing 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 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 syndrome because very high cortisol levels may overwhelm 11β-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. Primary pigmented nodular adrenocortical disease (PPNAD) is a distinctive form of ACTH-independent Cushing 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 centrofacial lentigines 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. Genetic loci for Carney complex have been mapped to the gene for the type 1α regulatory subunit of protein kinase A (PRKAR1A) on chromosome 17q22–24 [45] and less frequently to chromosome 2p16. Patients with Carney complex and PRKAR1A mutations generally develop PPNAD as adults, and those with the disorder mapping to chromosome 2 (and most sporadic cases) develop PPNAD less frequently and later. 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 [46] or PDE11A [47]genes encoding different phosphodiesterase isozymes.

ACTH-independent Cushing 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, $G_s\alpha$, through which the ACTH receptor (MCR2) normally signals. This results in inhibition of guanosine triphosphatase activity and 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 bone (producing fibrous dysplasia), gonads, thyroid, and pituitary. Clinical manifestations depend on which tissues are affected.

In summary, where the genes causing nodular adrenocortical hyperplasia have been identified, they all produce overactivity of the ACTH signaling pathway either by constitutively activating $G_s\alpha$ (McCune-Albright syndrome), by reducing the breakdown of cAMP and thus increasing its intracellular levels (mutations of PDE8B or PDE11A), or by disrupting the regulation of the cAMP-dependent enzyme, protein kinase A (PRKAR1A mutations).

Additionally, 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. Adrenocortical carcinomas can occur in infancy or later in childhood in patients with Li-Fraumeni syndrome, which is caused by heterozygous mutations in the TP53 tumor-suppressor gene on chromosome 17p13.1.

Clinical manifestations. The disorder appears to be more severe and the clinical findings are more flagrant in infants than in older children. The face is rounded, with prominent cheeks and a flushed appearance (moon facies). Generalized obesity is common in younger children. Hypertension is common (occurring in approximately half of affected children) [48] 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 secondary 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 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 syndrome [49, 50].

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 μg/kg (maximum of 2 mg) given at 11 p.m. results in a plasma cortisol level of less than 5 μg/dL at 8 a.m. the next morning in normal individuals but not in patients with Cushing syndrome. It is prudent to measure the dexamethasone level in the same blood sample to ensure adequacy of dosing [49, 50].

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 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, 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 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 μg/kg/24 h in four divided doses, on consecutive days. In children with pituitary Cushing syndrome, the larger dose, but not the smaller dose, suppresses serum levels of cortisol. Typically, patients with ACTH-independent Cushing

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 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 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 syndrome occur in patients with generalized glucocorticoid resistance [51]. 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 disease in children [52, 53]. 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 disease in adults; remissions are usually not sustained after discontinuation of therapy. Experience with this agent is limited in children [54], 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.

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^2/24 h in three divided doses after the immediate postoperative period) is required until there is recovery of the hypothalamic–pituitary–adrenal axis.

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, a deiodinase enzyme can convert T4 to T3 [55].

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 [56, 57].

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, 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 [58]. Most importantly in the context of this chapter, they regulate sensitivity to catecholamines in both the cardiovascular and nervous systems [59]. 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 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). 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 antithyroglobulin – 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 [60]. Thioamide 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 [61]. Methimazole frequently causes rashes or other allergic reactions and may rarely 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, and approximately one quarter 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 and usually require thyroid replacement with levothyroxine.

The 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 [62]. 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 [63]. 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 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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Neonatal and Infant Hypertension

26

Janis M. Dionne

Abstract

Neonatal hypertension as a clinical entity has been recognized since the 1970s (Adelman Ped Clin North Am 25(1):99–110, 1978), and yet we still do not have a complete understanding of the physiologic blood pressure changes occurring over the first year of life. Measurement techniques have evolved to less-invasive blood pressure monitoring in a population with increasing complexity related to technologic advances. This chapter will focus on proper assessment of infant blood pressure, expected changes in blood pressure during the first year of life, as well as evaluation, management, and follow-up of neonatal and infant hypertension.

Keywords

Neonatal • Infant • Blood pressure • Hypertension • Incidence • Risk factors • Etiology • Evaluation • Management

Abbreviations

ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin-converting enzyme
ECMO	Extracorporeal membrane oxygenation
HP	Hewlett-Packard
IV	Intravenous
MAP	Mean arterial pressure
NICU	Neonatal intensive care unit
PDA	Patent ductus arteriosus
RAAS	Renin-angiotensin-aldosterone system
RVT	Renal vein thrombosis
UAC	Umbilical artery catheter
VLBW	Very low birth weight infants

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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 artery and radial or posterior tibial arteries, which have all demonstrated comparable blood pressure values in this population [2]. Direct intra-arterial monitoring may be necessary in the most acutely ill neonates

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although there has been a shift to noninvasive blood pressure monitoring for the majority of the neonates within a neonatal intensive care unit (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 pressure oscillations within the artery determining the mean arterial pressure (MAP) when the oscillations are maximal. The machine then uses an algorithm specific to each device to calculate systolic and diastolic blood pressure. 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 [3]. Even in premature infants, these noninvasive blood pressures correlate well with intra-arterial monitoring [4].

As each oscillometric blood pressure monitor uses independent algorithms for determination of blood pressure values, several studies have compared multiple devices for accuracy. Dannevig and colleagues compared three monitors: Dinamap Compact™, Hewlett-Packard™ (HP), and Criticare™ models. When compared to intra-arterial blood pressures, they found that the HP 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 [5]. The HP™ 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 3.3–8.4 mmHg [6]. Oscillometric devices overestimating low blood pressure were confirmed in a study of critically ill premature neonates that 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 leading to potential under-recognition of hypotensive events [7].

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 [8]. 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 [9]. 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 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 [10]. The elevation of blood pressure with feeding is relatively consistent with an increase of up to 20 mmHg. This observation has been confirmed in more recent studies with 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 [11]. In follow-up clinics of infants and children 1–3 years of age, the non-calm state has been associated with significantly higher blood pressures (17–30 mmHg

Table 26.1 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 asleep or quiet awake state
• Three blood pressure readings at 2 min intervals
• (1.5 h after feed or medical intervention)

Adapted from [16]

higher) than when the infant is calm [12]. It is 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 blood pressure assessment factors into clinical decision making. Some authors suggest that the median of three oscillometric blood pressure measurements should be used [13] while others state that one blood pressure during routine vitals is adequate, in calm healthy term newborns [14]. 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 [15]. Use of a standard protocol for newborn blood pressure measurement has been suggested by Nwankwo and colleagues [16] (see Table 26.1). 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. In addition, the first blood pressure reading was significantly higher than the third reading. Other than waiting for one and a half hours after a feed or medical intervention to take a blood pressure reading, the protocol is reasonable for use within the NICU setting, especially when clinical assessment and 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, and while this is discussed in more detail in Chap. 7 on Perinatal Programming, it also deserves brief mention here. Maternal blood pressure and/or hypertension have been related to higher newborn blood pressures in several studies [17–19]. In an early study, a significant correlation was found for blood pressure of maternal-infant pairs after delivery and at 1 year of age [20]. Maternal age has been positively correlated with newborn blood pressure in one study [17] but not consistently in other studies [21, 22]. Maternal diabetes may be related to higher newborn blood pressure especially when born earlier in gestation [19]. The effect of maternal smoking on infant and childhood blood pressure are conflicting, but a more recent birth cohort study demonstrated male infants of maternal smokers had blood pressures more than 8 mmHg higher than maternal nonsmokers, although the increase was not seen in female offspring [23]. The prenatal exposure to "second-hand smoke" seems to lead to alterations in infant circulatory control mechanisms [24]. In a Nigerian study of term neonates, maternal body mass index > 30 and low socioeconomic status were associated with higher newborn systolic blood pressure, although birth weight was still the strongest predictor of neonatal blood pressure [22]. Likely, even maternal nutritional intake has an effect on infant blood pressure, and early findings suggest a u-shaped curve for infant blood pressure at 6 months of age and maternal carbohydrate intake with the highest blood pressures in infants whose mothers' carbohydrate consumption was in the lowest and highest quartiles of intake [25]. Maternal protein intake does not seem to have the same effect [26].

Perinatal events may also influence newborn blood pressures with the most controversial being antenatal steroids administered during threatened preterm delivery. Antenatal steroids given within 7 days of birth can reduce respiratory distress syndrome, but the effect on newborn blood pressure has been controversial, with some studies finding higher newborn blood pressures [18, 27], while others did not [28, 29]. 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

[30]. 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 may influence infant blood pressure [31]. Maternal hemolysis, elevated liver enzymes, and low platelets or HELLP syndrome have been associated with lower blood pressures in neonates [27]. Even the mode of delivery and type of maternal anesthetic may have an impact on newborn blood pressures, with elective caesarean section and spinal anesthesia being related to lower systolic blood pressures in newborns [21].

The most strongly correlated intrinsic or infant factors consistently 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 demonstrating lower newborn blood pressure with lower gestational age [32, 33]. This same relationship has been shown for birth weight and blood pressure as most neonates who are born premature are also born at a low birth weight, but being born small for gestational age may also be associated with lower initial blood pressure values [32–34]. 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 substances on neonatal blood pressure is demonstrated in infant pairs of twin-twin transfusion syndrome where newborn blood pressures in recipients are significantly higher than donors [35]. In fact, 14 % of twin-twin transfusion recipients are hypertensive.

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 gestation during neonatal and follow-up periods [28]. Likely all these various factors, including antenatal and postnatal exposures, cumulative time with the exposure, gestational age, clinical condition, and genetic predisposition, interact in complex ways to influence neonatal blood pressures.

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 [32]. Their blood pressure nomograms have been the most widely used reference values, but 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 % confidence limits, which may be a better reference for newborn blood pressure values [33] [see Fig. 26.1].

First Days of Life

In very low birth weight infants (VLBW), systolic, diastolic, and mean blood pressure increase by more than 30 % over the first few days of life which demonstrates the physiologic changes that occur as neonates adapt to the ex utero environment [29]. 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 [29, 36]. 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 [32]. 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 [37].

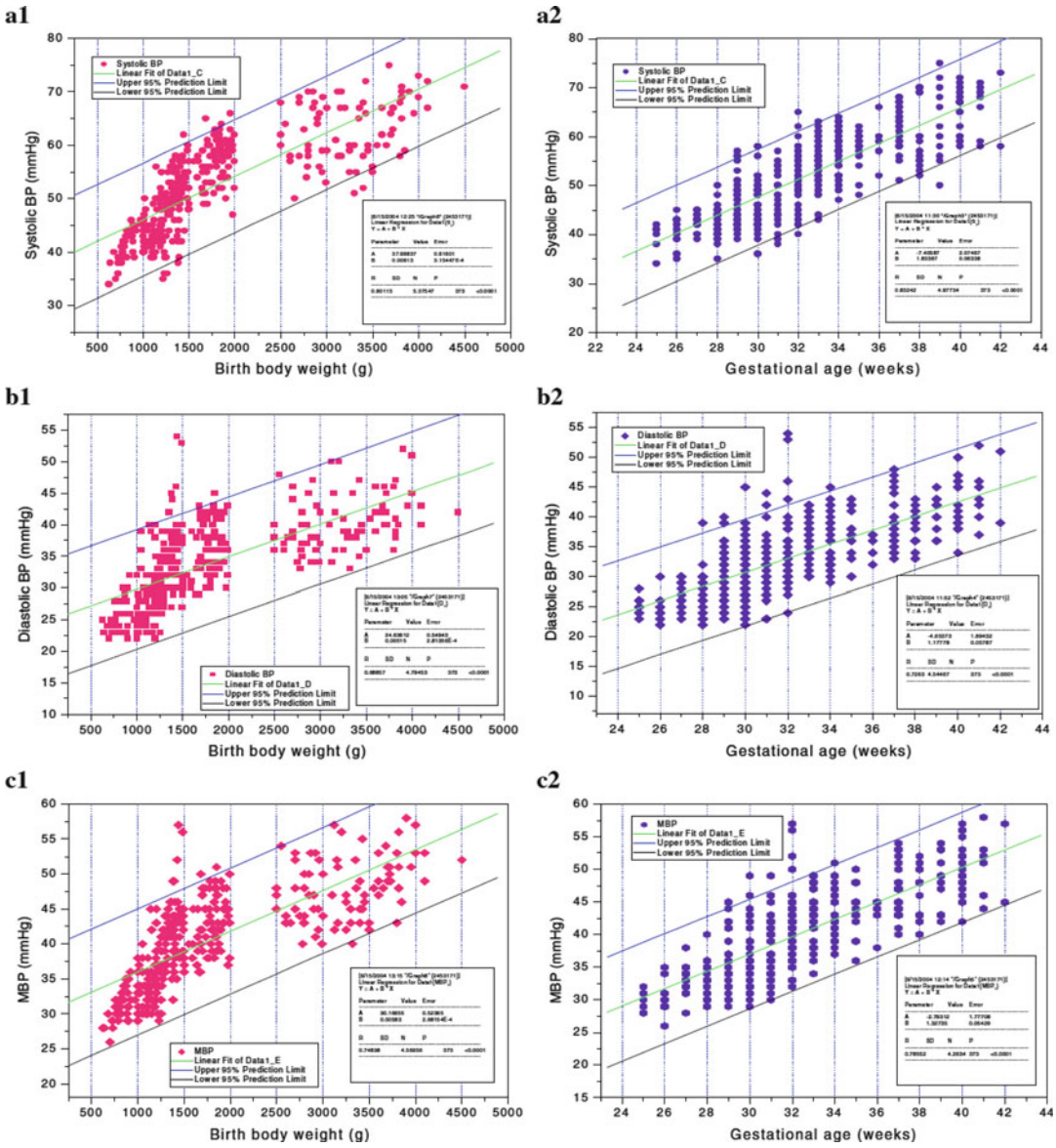

Fig. 26.1 *Neonatal blood pressure on day 1 of life is positively correlated with birth weight* (1) *and gestational age* (2). Systolic (**a**), diastolic (**b**), and mean (**c**) blood pressures are presented with 95 % confidence limits (Reproduced from Pejovic et al. [33] with kind permission from Springer Science + Business Media)

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 based on gestational age at birth or birth weight. The study by Pejovic and colleagues found that the neonates with the lowest gestational age at birth had the most rapid rate of rise of blood pressure with an average increase in mean blood pressure of 26 % in the first week and 51 % in the first month in infants born at less than 28 weeks

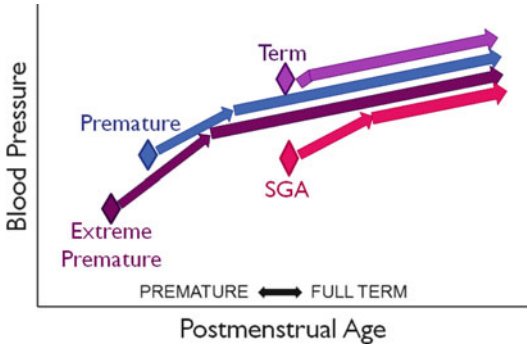

Fig. 26.2 Illustration of patterns of neonatal blood pressure changes when born at term or premature, extremely premature, or small for gestational age (SGA)

gestational age compared to 13 % and 22 % in full-term infants [33]. 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 gestational age had a rapid increase in blood pressure over only 1 week [38]. The authors suggested that the blood pressure values at the end of the rapid increase were similar to term infants in the first days of life.

These studies are consistent with an earlier study that determined VLBW infants had similar blood pressure values to other NICU graduates at 4 months corrected age despite remaining smaller in length and weight [39]. As blood pressures were not measured between discharge and 4 months of age, we do not know when the catch-up occurred. The appropriateness of weight at birth and blood pressure was assessed in a study of full-term newborns whose birth weights varied from < 2,500 to > 3,500 g [34]. They found that the term infants with the lowest birth weights had the lowest blood pressures initially but then had the most rapid rate of rise of blood pressure so that by 1 month of age, all term infants had similar blood pressures that remained comparable throughout the first year of life. This multitude of variations in blood pressure patterns over the first weeks of life is represented in Fig. 26.2

Infant blood pressures have also been described as increasing with postconceptional age (gestational age plus postnatal age) which is now referred to as postmenstrual age. The Philadelphia Study Group developed a clinically useful graphical reference of blood pressure by postconceptual age to be used in neonates after the first day of life while still in the neonatal and early infant period [32]. Recognizing that infant blood pressures over the first 2 weeks are rapidly changing and could influence nomograms by postmenstrual age, we recently derived normative values for infant blood pressures after 2 weeks of life based on current postmenstrual age from the available published literature [40, 41] [see Table 26.2]. 95th and 99th percentiles were calculated as a reference for clinicians to use to determine which infants may require treatment (discussed in more detail later in this chapter).

First Year of Life

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 1980s [42] [see Fig. 26.3]. Unfortunately, the infant blood pressures were measured using the Doppler method, which likely provides slightly lower readings than by the oscillometric method commonly used today. As well, the diastolic blood pressures are less likely to be reliably determined with Doppler method so that the number of readings is less than systolic, although this reference still provides data based on the largest number of infants to date (systolic $n = 7{,}643$, diastolic $n = 3{,}048$). 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 values over the first year of life [43] [see Fig. 26.4]. The blood pressures were only measured on day 2 of life, at 6 and 12 months of age and therefore do not provide normative data for ages in between, but the advantage is that the blood pressures were measured using the most commonly used method today.

Table 26.2 *Infant blood pressures by postmenstrual age after 2 weeks of life;* systolic (SBP), mean (MAP), and diastolic (DBP) blood pressures are presented by 50th, 95th, and 99th blood pressure 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 [41]

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, but as we now know, values vary based on factors such as gestational age, birth weight, and postnatal age. As studies were published of normative values with percentiles, such as Zubrow and the Philadelphia Neonatal Blood Pressure Study Group or the Second Task Force Report on Blood Pressure, then clinicians applied the concepts used in studies of older children and adopted the 95th percentile blood pressure as the definition of hypertension [32, 42]. Unfortunately, we do not have outcome studies in infants to support or refute the use of this arbitrary definition of

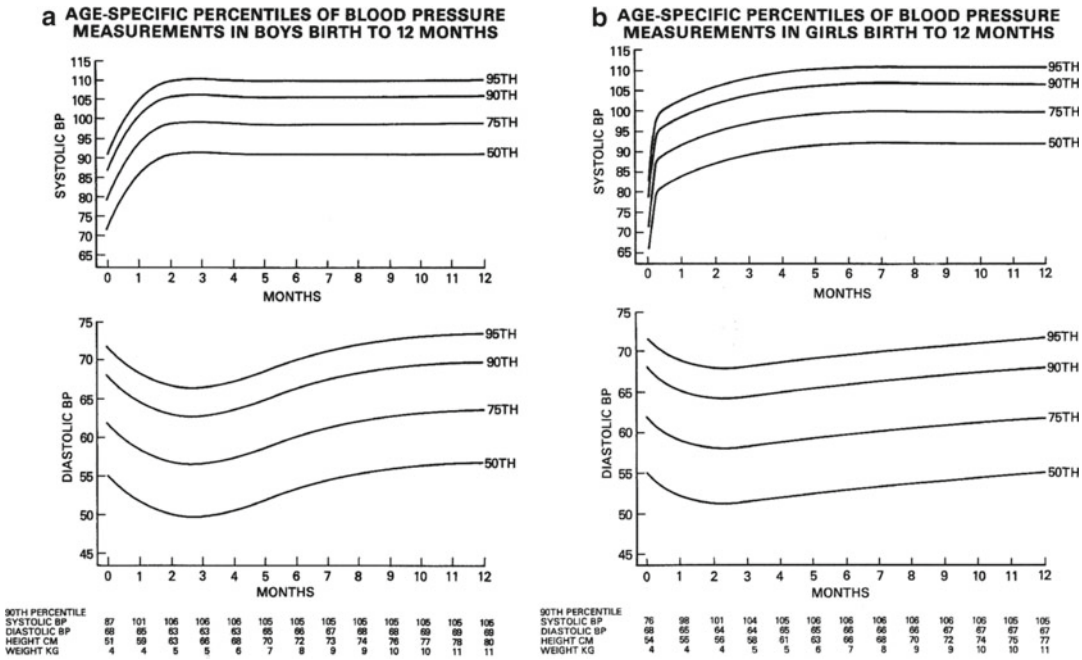

Fig. 26.3 Blood pressure percentiles for (**a**) male infants and (**b**) female infants from birth to 12 months of age (Reprinted from the Task Force on Blood Pressure Control in Children [42])

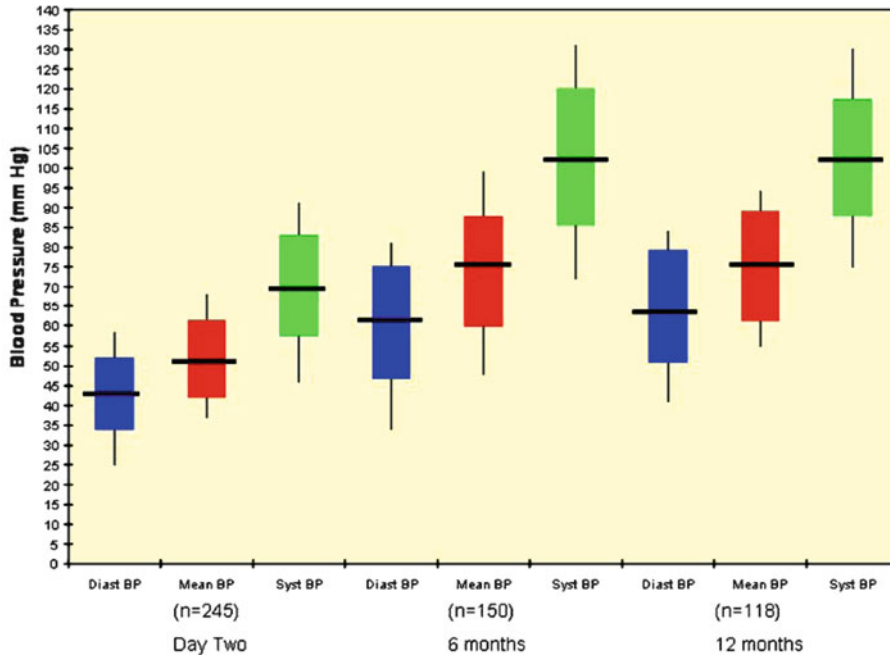

Fig. 26.4 *Healthy term infant blood pressure values by oscillometric method at 2 days, 6 months, and 12 months of age.* Diastolic (*blue*), mean (*red*), and systolic (*green*) values are indicated with the median (*horizontal bar*) and 5th to 95th percentiles (*box*) (Reproduced from Kent et al. [43] with kind permission from Springer Science + Business Media)

hypertension although in the future this may come from the neurocognitive or cardiovascular literature [44, 45]. In addition, the use of antihypertensive medications in the neonatal and infant population is associated with defined risks, and very few studies have been completed on use of blood pressure medications 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 [41] [see Table 26.2]. In infants, blood pressure values consistently above the 95th percentile based on curves from the Second Task Force on Blood Pressure [see Fig. 26.3] or oscillometric values from the study by Kent and colleagues [see Fig. 26.4] should be considered as hypertension and investigated and managed as appropriate [42, 43].

Incidence of Hypertension

The incidence of hypertension in general healthy newborns is low, likely around 0.2 %, and routine screening of blood pressure is recommended only in infants considered "at risk" which includes NICU graduates, infants with congenital heart or kidney disease, or with other childhood diseases [46, 47]. In one of the first studies of neonatal hypertension, Adelman found an incidence of 2.5 % of NICU infants when hypertension was defined as a blood pressure > 90/60 mmHg in term infants or > 80/45 mmHg in preterm infants [1]. Other NICU studies have found a lower incidence between 0.7 % and 0.8 % [48, 49]. A recent Australian study of all newborns admitted to a tertiary level NICU found an incidence of neonatal hypertension of 1.3 % when more than 2,500 infants were reviewed [18]. 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 [48]. 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 [50]. 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 of hypertension 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. In an earlier study by Singh and colleagues, risk factors for hypertension included use of an umbilical artery catheter (UAC), chronic lung disease, patent ductus arteriosus, and intraventricular hemorrhage [49]. In the Australian study mentioned previously, risk factors for hypertension included acute renal failure, UAC, maternal hypertension, antenatal steroids, and lower gestational age with 76 % of the neonates with hypertension being premature [18]. In the large database study by Blowey and colleagues, the risk of hypertension was higher in infants with acute or chronic renal failure, congenital anomalies of the kidneys and urinary tract, intraventricular hemorrhage, neonatal asphyxia, seizures, necrotizing enterocolitis, UAC, and lower birth weight, and in those infants requiring extracorporeal membrane oxygenation (ECMO) [50]. Hypertension was also more common in infants with a higher severity of illness score, those with more coexisting diagnoses, longer lengths of hospital stay, and in infants that expired before discharge reflecting a more complex and ill population.

Causes of Hypertension

The most common etiologies of neonatal hypertension are renovascular and renal parenchymal disease, accounting for 50 % of cases [49] [see Table 26.3]. The most common renovascular causes include renal artery thrombosis, renal artery stenosis, and renal vein thrombosis (RVT), all of which may be idiopathic but are more often related to use of umbilical catheters. 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 monogenic forms of hypertension.

Table 26.3 Causes of neonatal and infant hypertension

Renovascular	**Neurologic**
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	**Endocrine**
Renal myofibromatosis	Congenital adrenal hyperplasia
Renal parenchymal	Cushing's syndrome
Congenital	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	**Neoplastic**
Renal tubular dysgenesis	Neuroblastoma
Atypical hemolytic uremic syndrome	Wilms tumor
Associated with urologic anomaly	Mesoblastic nephroma
Ureteropelvic junction obstruction	Adrenocortical carcinoma
Obstructive uropathy	**Medications/drugs**
Neurogenic bladder	*Maternal*
Megaureter	Cocaine
Acquired	Heroin
Acute tubular necrosis	*Infant*
Cortical necrosis	Corticosteroids
Pyelonephritis	Adrenergic agents
Interstitial nephritis	Caffeine
Nephrocalcinosis	Theophylline
Heritable hypertension	Phenylephrine
Liddle syndrome	Erythropoietin
Apparent mineralocorticoid excess	Pancuronium
Glucocorticoid-remediable aldosteronism	Vitamin D intoxication
Cardiovascular	**Other causes**
Coarctation of the aorta	Excess salt/saline intake
Patent ductus arteriosus	Hypercalcemia
Congenital aortic aneurysm	Total parenteral nutrition
ECMO	Closure of abdominal wall defect
Respiratory	Adrenal hemorrhage
Chronic lung disease	Traction

The association between UACs and renal artery thrombosis has been recognized for decades [1]. The mechanism is likely related to disruption of the vascular endothelium by the catheter with subsequent development of thrombus and an associated risk of 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 [51]. Seibert and colleagues 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 [52]. 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 [53].

Renal artery thrombosis is most commonly associated with 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 % [18, 49, 50]. In the study by Singh and colleagues, 35 % of hypertensive infants with a UAC had associated thrombocytopenia and 25 % had lower limb ischemia [49]. 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, but 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 [54]. Renal venous thrombosis 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 predominance for the left kidney and male infants [55, 56].

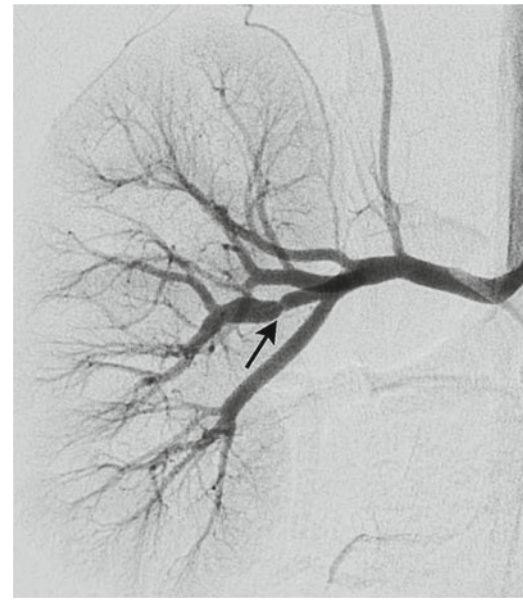

Fig. 26.5 *Renal angiogram* demonstrating renal artery stenosis of a second-order renal artery branch with post-stenotic dilation (Reproduced from Vo et al. [108] with kind permission from Springer Science + Business Media)

Renal arterial stenosis may be a complication of a UAC, or it may be related to fibromuscular dysplasia, mid-aortic syndrome, or external compression by a mass, or, less commonly in infants, associated with a vasculitis or disease syndrome such as neurofibromatosis or Williams' syndrome [57] [see Fig. 26.5]. Other uncommon causes associated with renal artery stenosis include congenital rubella syndrome, renal myofibromatosis, and idiopathic arterial calcification of infancy [58–60]. 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.

In hypertensive neonates within the NICU, between 25 % and 40 % will have a renal abnormality on ultrasound [18, 49]. Lanzarini and colleagues 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 [61]. Congenital renal diseases associated with hypertension include polycystic kidney disease (both autosomal dominant and recessive) and renal dysplasia in isolation or

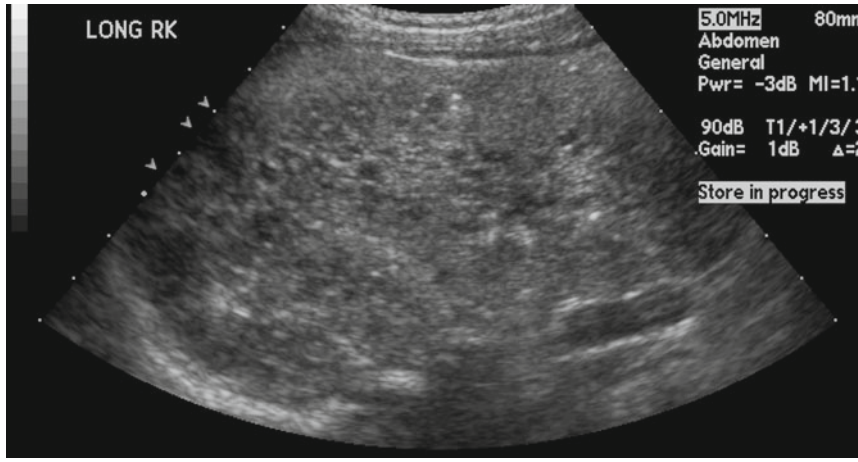

Fig. 26.6 *Renal ultrasound* image demonstrating an enlarged echogenic kidney with lack of corticomedullary differentiation and numerous microcysts consistent with autosomal recessive polycystic kidney disease

associated with urologic abnormalities such as posterior urethral valve or vesicoureteral reflux, renal hypoplasia, multicystic dysplastic kidney, congenital or infantile nephrotic syndrome, and uncommonly 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 [62] [see Fig. 26.6]. The median age at diagnosis of hypertension in these patients is 16 days old, and hypertension is common in infants also presenting with hyponatremia which may reflect severe tubular dysregulation. The hypertension may be challenging to treat and often requires multiple agents [62]. Even autosomal dominant polycystic kidney disease, where complications are less common during childhood, can cause hypertension in infants less than 1 year of age [63]. Multicystic dysplastic kidneys rarely cause hypertension as they are thought to be nonfunctional but in some cases seem to have just enough renal blood flow or function to cause severe hypertension, likely renin mediated, and in these cases the hypertension resolves after nephrectomy [64]. Renal dysplasia may be associated with hypertension and is common in obstructive uropathies such as posterior urethral value and prune belly syndrome but may not be 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 [65]. Other urologic abnormalities associated with infant hypertension include megaureter and neurogenic bladder, often in infants with a meningomyelocele [61, 66].

Acquired renal causes of infant hypertension are less common but may include acute tubular necrosis related to moderate hypoxic, hypotensive, or nephrotoxic injury to the kidneys or if more severe injury, kidneys may develop cortical necrosis. Other acquired causes of renal parenchymal disease and infant hypertension include pyelonephritis, interstitial nephritis, and nephrocalcinosis [48, 67, 68]. Rare heritable forms of hypertension such as Liddle syndrome, apparent mineralocorticoid excess, and glucocorticoid-remediable aldosteronism may present during infancy, and clinical suspicion based on family history and/or suppressed plasma renin is important to diagnose these rare causes as treatments are directed at the specific underlying pathophysiology [69, 70].

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 and 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 [71]. This group is also at risk of restenosis and recurrent hypertension during childhood, and therefore, these children need careful long-term follow-up as systolic blood pressure has been correlated with residual obstruction and may be a clue to persistent stenosis [72]. Patent ductus arteriosus (PDA) as well as closure of the PDA have been associated with neonatal hypertension [1, 49]. 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 aorta.

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, when hypertension was defined as systolic blood pressure greater than 90 mmHg, and 44 % of infants developed intraventricular hemorrhage [73]. 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 [74, 75]. A more recent 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 [76]. The mechanisms are thought to involve alterations in the baroreflex and modulation of hormones [77].

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 12 % to 43 % with an average age of onset of 3.5–5.9 months with approximately half of cases occurring after discharge from the NICU [78–80]. In addition, some infants with chronic lung disease, or at risk of developing chronic lung disease, are treated with corticosteroids or other medications for a period of time which can cause or exacerbate hypertension [81].

Infant hypertension may also be found in disorders of the neurologic and endocrine systems as well as in association with various tumors. 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 [82]. Hypertension occurs in about 3 % of infants with intraventricular hemorrhage [49, 50]. Premature neonates are at particular risk due to the delicate germinal matrix in the brain, and intracranial hypertension may also develop after neonatal asphyxia [83]. Unfortunately, the clinical signs of systemic hypertension and intraventricular hemorrhage may be indistinguishable and include irritability, lethargy, apnea, hypotonia, seizures, and coma [1]. 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 related to deficiencies in either 11β-hydroxylase or 17α-hydroxylase leading to over production of deoxycorticosterone which has mineralocorticoid activity [84, 85]. Other endocrine causes of hypertension include Cushing's syndrome, neonatal hyperthyroidism, hyperaldosteronism, and pheochromocytoma [86–89]. Several neoplastic causes of infant hypertension have been recognized including Wilms tumor, neuroblastoma, and mesoblastic nephroma which may all present during infancy [90–94]. 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 related to maternal ingestion, as in cocaine or heroin abuse, or medications may be prescribed to infants within the NICU for a specific indication [95, 96]. Infants with chronic lung disease may be treated with corticosteroids, caffeine, or theophylline, all of which may lead to hypertension [97, 98]. Vitamin D intoxication has been associated with infant hypertension although it is not clear if this is related to hypercalcemia or some other mechanism [46]. Excess saline administration or salt intake may increase blood pressures in neonates [46, 99]. 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.

Diagnostic 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 [1]. 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 [100]. Neurologic symptoms may be indistinguishable from intracranial hemorrhage and may include lethargy, apnea, tremors, opisthotonus, facial palsy, hemiplegia, seizures, and coma [1, 101]. Infants may be oliguric or polyuric with renal parenchymal or renovascular abnormalities [46]. Clinical signs and symptoms may provide clues to both the severity and the cause of the elevated blood pressure.

Table 26.4 Diagnostic investigations for neonatal and infant hypertension

Common investigations	Specific investigations
Urinalysis	Plasma renin activity, aldosterone
Serum electrolytes (Na, K, Cl, HCO_3)	Head ultrasound
Blood urea nitrogen, creatinine	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_3* bicarbonate, *DTPA-Tc 99m* diethylenetriamine pentaacetic acid, *MAG3-Tc 99m* mercaptoacetyltriglycine

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 newborns have had complications in early life or when there is a history of hypertension at a young age. Fortunately, for infants within the NICU, 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 evaluation of the infant is to confirm the blood pressure elevation by using a standardized blood pressure measurement technique [see Table 26.1] and ensuring the proper cuff size is used. 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 26.3] as well as looking for signs of end organ damage including cardiac and neurologic abnormalities. Although procedurally challenging, signs of hypertensive retinopathy may be present even in neonates with hypertension [102]. Abdominal examination is critical in these infants and should include inspection, auscultation for

bruits, and palpation of the size and symmetry of the kidneys and detection of masses.

Investigations should be tailored to the degree of hypertension and information gathered on history and physical examination. Basic laboratory investigations could include urinalysis, serum electrolytes, blood urea nitrogen, creatinine, and complete blood count [see Table 26.4]. Renal ultrasound with Doppler is a high yield initial investigation in this population. Renal parenchymal abnormalities, such as polycystic kidney disease and renal dysplasia, and structural abnormalities, such as ureteropelvic junction obstruction, are easily diagnosed with basic renal ultrasonography. It is important to note that renal echogenicity and corticomedullary differentiation are relatively increased in neonates [103], 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, but Doppler imaging is 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. In infants presenting with heart failure of unknown etiology, hypertension as a cause may be suspected by reduced left ventricle systolic function without chamber enlargement, increased left ventricular mass, diastolic dysfunction without left atrial dilatation, and aortomegaly with Doppler suggestive of increased vascular resistance [104]. Infants may not be hypertensive at presentation when cardiac function is compromised but develop high blood pressure as cardiac function improves, although afterload reduction may improve both blood pressure and cardiac function [104].

Plasma renin 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 higher in preterm than term infants [105, 106]. 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 [105]. A suppressed plasma renin may be suggestive of a monogenic form of hypertension, while an elevated renin may suggest a renal stenosis or thrombosis although 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 [107].

When renovascular hypertension is suspected, angiography may be the best investigation but is not always feasible. A review of renal angiography in a select group of hypertensive children without comorbid conditions revealed that 90 % had a single stenosis with only 25 % in the main renal artery, 50 % in a second order renal artery, and the remainder in more distal branches or accessory vessels indicating the importance of angiography for detection of most renal artery stenoses [108] [see Fig. 26.5]. 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 [57, 107]. Unfortunately, these procedures require a general anesthetic and may be technically challenging in small infants, and therefore, infants are often managed medically until they achieve a size where the procedure is technically feasible. Other imaging techniques include computed tomography angiography or magnetic resonance angiography, although they are not good at detection of intrarenal vascular anomalies which are often present in infants [103]. Consideration must also be given to a prothrombotic workup in infants with proven thromboses as clotting factor abnormalities are common in infants with renal vein thrombosis regardless of other predisposing perinatal conditions [56, 109].

Management

Hypertensive crises are life-threatening emergencies that require prompt and careful management to avoid complications either of the hypertension or of the treatment and therefore 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 [101]. Several classes of antihypertensive agents have been used in infants for management of severe hypertension including vasodilators, ACE inhibitors, calcium channel blockers, and α- and β-antagonists [see Table 26.5]. 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. There is one case series of IV enalaprilat use in neonates, but given the high incidence of side effects, importance of the renin-angiotensin-aldosterone system (RAAS) in neonates, and lack of established dose, we cannot endorse its use [110]. 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 [111, 112]. 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 [113]. Side effects of labetalol included hypoglycemia, bradycardia, and hypotension, although the adverse events were not more common than in the other drug classes, but 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 [114, 115].

Unfortunately, there are occasions when intravenous infusions are not immediately available and other agents must be used. Hydralazine may be given IV or orally with a short onset of action of 5–20 min for IV administration and 20–30 min when given orally. Nifedipine has been studied in infants with hypertensive crises at a dose of 2.5 mg with good effect [116] although 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 dispensed 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 [117, 118]. Other fast-acting medications to consider include oral captopril, clonidine, and minoxidil [47] [see Table 26.5]. Some of these agents may not be available in all countries, so one's choice of agent may be partly driven by what is available.

As with many medications in pediatrics, most antihypertensive drugs are not approved for use in children, particularly infants, as adequate studies have not been conducted involving this age group [119]. In neonates, the physiology of the immediate postnatal life is very different from older children, and therefore, 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, but small studies of other antihypertensive medications can be used for guidance when trying to manage infant hypertension. Captopril, a short-acting ACE inhibitor, is much more potent in neonates, and they require a lower dose for clinical effect [see Table 26.5]. Infants may have significant decreases in blood pressure associated with captopril as well as acute renal failure and neurologic consequences [120]. Similar caution should be used for longer-acting ACE inhibitors such as enalapril, lisinopril, and quinapril when used in infants. In addition, we are learning more about the importance of the RAAS during renal development [121], and concern has been raised about persistent use of inhibitors of this developmentally important system in neonates and long-term consequences that have yet to be determined.

Table 26.5 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: 5 mg/kg/day	Q 4–6 h TID to QID	May cause tachycardia, fluid retention, diarrhea, emesis, agranulocytosis
	Minoxidil (PO)	0.05–2.0 mg/kg/day	BID	May cause tachycardia, fluid retention, hypertrichosis
ACE inhibitors	Captopril (PO)	Neonates: Initial: 0.01 mg/kg/dose Max: 1.5 mg/kg/day Infants: Initial: 0.1–0.3 mg/kg/dose Max: 6 mg/kg/day	 TID to QID BID to TID	May cause hypotension, oliguria, acute renal failure, hyperkalemia, neurologic complications
	Enalapril (PO) Lisinopril (PO) Quinapril (PO)	Infants: 0.1–0.6 mg/kg/day 0.1–0.5 mg/kg/day Initial: 0.1–0.2 mg/kg/day	Daily to BID Daily Daily	All may cause hypotension, oliguria, acute renal failure, hyperkalemia, agranulocytosis, angioedema. Caution in preterm neonates
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: 0.1 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)	Initial: 0.25 mg/kg/dose Max: 2.5 mg	Q 4–6 h	May cause hypotension, tachycardia, transient neurologic changes
α- and β-antagonists	Labetalol (IV) Labetalol (PO) Carvedilol (PO)	0.2–1.0 mg/kg/dose 0.25–3.0 mg/kg/h 1.0–10 mg/kg/day 0.05–0.4 mg/kg/dose	Load Infusion BID BID to TID	May cause hypotension, hyperkalemia. Caution in chronic lung disease, heart block, unstable heart failure May cause hypotension, bradycardia, edema, hyperglycemia
β-Antagonists	Esmolol (IV) Propranolol (IV) Propranolol (PO)	125–1,000 mcg/kg/min 0.01–0.15 mg/kg/dose 0.5–6 mg/kg/day	Infusion QID BID to QID	All may cause hypotension, bradycardia. Caution in chronic lung disease, unstable heart failure
α-Antagonist	Prazosin (PO)	Initial: 5 mcg/kg/dose 25–400 mcg/kg/day	TID to QID	May cause hypotension, somnolence
Central α-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	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

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 [122]. Isradipine, a second-generation dihydropyridine calcium channel blocker, has been used in hospitalized neonates, infants, and children with good effect [117, 118]. 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.

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 [1]. In an Australian study of neonates with hypertension, 82 % were treated during the initial hospitalization and the most commonly prescribed medications were hydralazine, followed by captopril, labetalol, and atenolol [18]. This is consistent with observed management in the large database study by Blowey and colleagues where vasodilators, primarily hydralazine, were prescribed in 64 % of infants, ACE inhibitors in 51 %, then calcium channel blockers (24 %), alpha- and beta-blockers (18 %), and clonidine (5 %) [50]. Medications were prescribed at a median age of 15 days of life, the median duration was 10 days, and 45 % were treated with two or more drugs [50].

In some cases, surgical or interventional management can be curative for hypertension in infants. For renal artery stenosis, percutaneous transluminal renal angioplasty to correct the stenosis may be curative when the lesion is unilateral and not associated with a systemic disease process although the procedure is technically more difficult in small infants who are often managed medically awaiting further growth [57, 107]. Surgical correction of coarctation of the thoracic aorta improves blood pressure in many but not all infants with this congenital malformation [71]. For infants with tumors such as Wilms tumor, neuroblastoma, and mesoblastic nephroma, surgery usually results in normalization of the blood pressure [90, 92, 94]. Rarely structural or function anomalies of the kidney and urinary tract associated with severe hypertension may require surgery, and it has been reported as curative in some cases of ureteropelvic junction obstruction, multicystic dysplastic kidney, and unilateral renal hypoplasia [64, 67, 123, 124]. 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 [125].

Long-Term Outcome

Few follow-up studies of neonatal hypertension have been published. The review published by Adelman in 1978 of 17 infants with neonatal hypertension found that 13 (76 %) were normotensive off antihypertensive medications by 3–6 months after the onset [1]. Results were similar in a slightly later study of infants hypertensive in the NICU where 56 % were normotensive within the first month of life, 67 % by 6 months of age, and 81 % by 1 year of age [48]. 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 [18].

Attention has been given to certain infant disease states with reported longer-term blood pressure outcomes. While in some conditions the blood pressures improve with time, others are associated with increasing hypertension.

Follow-up on infants discharged from the NICU with chronic lung disease has shown that infants with hypertension in the NICU or at follow-up had resolution of the elevated blood pressure at a mean of 7.8 months although the range was less than 1 month to just over 2 years [78]. 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 [125]. Several long-term studies of renal vein thrombosis during infancy have found kidney outcomes are poor regardless of treatment with 66–90 % showing irreversible kidney damage at follow-up and 19–34% of these patients had elevated blood pressure long term [55, 56, 109, 126]. Chronic renal failure was reported in around 30 %, proteinuria in 12 %, and urine-concentrating defects in almost 50 % [109, 126].

Another concern is for the development of hypertension in high-risk infants after discharge from the NICU. Sheftel and colleagues screened infants who were normotensive during the NICU course at follow-up clinics during the first year of life and found 9 % were hypertensive based on three separate systolic blood pressure readings [127]. After extending their cohort and follow-up period, they found 2.6 % were hypertensive at an average follow-up of 19 months [128]. 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. Another study followed up cohorts of VLBW infants at 1, 2, and 3 years of age and found that the observed systolic blood pressure value did not differ between cohorts but that the percentage with blood pressure values exceeding the 95th percentile decreased from 33 % at 1 year to 15 % at 2 years and 8 % at 3 years [129]. A study of genetic and clinical risk factors for infant hypertension found discharge on supplemental oxygen, history of urinary tract infection during NICU, and cytochrome P450 CYP2D6 'CC' genotype to be independent risk factors for elevated blood pressure at NICU follow-up clinics [28].

We should not be surprised that the risks for development of hypertension in this population are likely multifactorial as these infants are often born prior to completion of nephrogenesis and may be susceptible to acute kidney injury from hypoxia, hypotension, and nephrotoxins in addition to a possible genetic predisposition. Following on the early hypothesis by Brenner and colleagues that reduced nephron endowment predisposes to the development of hypertension [130, 131], Rodriguez and colleagues examined renal autopsy specimens from premature and term neonates and found that glomerulogenesis is decreased in all preterm infants and correlates with gestational age [132]. In addition, active glomerulogenesis is absent in longer surviving premature infants and is further inhibited by acute kidney injury. This provides further support to the clinical recommendation that surviving premature infants need long-term follow-up that includes blood pressure assessment.

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. 7 on Perinatal Programming of Blood 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 of perinatal factors compared to later health status. Studies that have followed up premature infants through childhood have found an increased incidence of hypertension (7–16 %), chronic renal insufficiency (11 %), and tubular dysfunction (10–15 %) in this population [133, 134]. 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 [135]. 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 [136]. As discussed above, hypertension may develop in children and adults who were born premature due to a reduced nephron endowment.

Several studies have shown that low birth weight or being born small for gestation age is inversely correlated with blood pressure in childhood and early adulthood and may be related to a higher prevalence of hypertension [137–139]. 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 [140]. ABPM in children born small for gestation age found blunted circadian and ultradian rhythms in addition to elevated blood pressure demonstrating altered cardiovascular regulation in children born growth restricted [141]. The exact mechanism for the higher cardiovascular risk may differ depending on the etiology as suggested in a 20-year follow-up study of premature neonates where offspring of hypertensive pregnancies showed impaired endothelial function and subclinical atherosclerosis compared to normotensive pregnancy preterm offspring who demonstrated increased aortic stiffness [142]. Differential vascular programming may influence 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 during childhood and adolescence, abnormal lipid profile in adolescents, and abnormal glucose metabolism in those children born small for gestational age suggesting effects of both prenatal and early postnatal programming [143, 144]. 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 [145]. Exclusive breast feeding of infants has been associated with lower childhood systolic blood pressure with a dose-response relationship in one study [146], while others did not find this association [147, 148] although breast feeding should still be encouraged for all the other health benefits. 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 adult body mass index [136, 138, 139, 148, 149]. This has lead 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 [139].

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 and more accurately determine abnormal values or hypertension. 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. The most common causes of hypertension remain renovascular, commonly related to umbilical catheters, renal parenchymal, coarctation of the aorta, and chronic lung disease although there are newer associations indentified such as ECMO. Most causes can easily be determined by infant history and some basic investigations, and more antihypertensive agents are being trialed or used within this population creating more options for treatment. Most neonatal

hypertension will resolve over time although some disease states that may be identified during infancy need long-term follow-up for the development of hypertension or other complications. 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.

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Obstructive Sleep Apnea and Hypertension

27

Alisa A. Acosta

Abstract

Obstructive sleep apnea (OSA) is the most severe form of sleep-disordered breathing (SDB) (Benninger and Walner, Clin Cornerstone 9:s6–12, 2007), which encompasses all forms of abnormal breathing during sleep (Marcus, Curr Opin Pediatr 12:208–12, 2000). Adults with OSA have a significant association with cardiovascular disease, specifically hypertension (HTN) (Somers et al. Circulation 118:1080–111, 2008). The relationship between systemic HTN and OSA is well documented (Lavie et al. BMJ 320:479–82, 2000, Nieto et al. JAMA 283:1829–36, 2000, Peppard et al. N Engl J Med 342:1378–84, 2000), and one particular prospective population study, the Wisconsin Sleep Cohort Study, documented OSA preceded and predicted the development of HTN (Peppard et al. N Engl J Med 342:1378–84, 2000). OSA has also been associated with drug-resistant HTN in adults (Grote et al. J Hypertens 18:679–85, 2000, Logan et al. J Hypertens 19:2271–7, 2001) which may be partially mediated by aldosterone (Calhoun et al. Chest 125:112–7, 2004, Pratt-Ubunama et al. Chest 131:453–9, 2007). The relationship between OSA and HTN is so well defined in adults that OSA is now recognized as an identifiable cause of HTN and should be considered during the evaluation for elevated blood pressure (BP) (Chobanian et al. Hypertension 42:1206–52, 2003). The National High Blood Pressure Education Program Working Group made a similar recommendation to screen for OSA as a comorbid condition in children with HTN (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, Pediatrics 114:555–76, 2004). However, the relationship between SDB and HTN is not as clear in children. Regardless, there is evidence to suggest an association between

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these two conditions. There is also evidence suggesting an independent effect of SDB on left ventricular geometry changes which improve after treatment of SDB. Obesity is a suspected confounder in the associations between SDB, HTN, and left ventricular geometry changes, but the interaction and causal relationship is still unknown.

Keywords
Sleep-disordered breathing • Sleep apnea • Hypertension • Blood pressure • Left ventricular hypertrophy • Children and adolescents

Definitions and Epidemiology of SDB

The American Thoracic Society defines OSA in children as a sleep-related breathing disorder "characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction (obstructive apnea) that disrupts normal ventilation during sleep and normal sleep patterns" [13]. Specifically, an *obstructive apnea* is a cessation in ventilation despite effort for 10 s or two breath cycles in older children or despite effort for 6 s or 1.5–2 breath cycles in infants [14]. An *obstructive hypopnea* is a decrease in airflow by at least 50 % despite effort occurring at the same time or during breath cycles associated with a desaturation or arousal [13]. Both of these events contribute to the apnea-hypopnea index (AHI), which is defined as the total number of apneas and hypopneas per hour of sleep (also referred to as the respiratory disturbance index, RDI) [14]. AHI can only be measured by polysomnography (PSG), the gold standard for diagnosing SDB. An AHI >1 is considered abnormal in children [15] contrary to adult guidelines which specify an AHI >5 as the cutoff for the diagnosis of OSA [16]. When partial upper airway obstruction results in hypercapnia, these episodes are referred to as *obstructive hypoventilation*. Obstructive hypoventilation requires measurement of end-tidal CO2 (ETCO2) and is defined by an ETCO2 >45 mmHg for more than 60 % of total sleep time or any ETCO2 >53 mmHg [15].

Another form of SDB is the upper airway resistance syndrome (UARS) characterized by partial obstruction of the upper airway leading to arousals and sleep fragmentation without gas exchange abnormalities [17]. UARS was first described in children in 1982, but the actual term was first used in reference to adults [18, 19]. Despite the lack of abnormal ventilation or oxygenation, excessive daytime somnolence is a common symptom among adults and children with UARS [18–21]. Children can also present with hyperactivity [18]. For the diagnosis of UARS, certain techniques and measurements are required during PSG. A nasal cannula/pressure transducer and an esophageal catheter can measure the esophageal pressure, allowing for the detection of more subtle changes in breathing patterns during sleep [21]. If an esophageal catheter is not available, UARS can be diagnosed by the presence of asynchronous movements of the chest and abdomen followed by arousal, but this paradoxical breathing can be a normal finding during sleep in children less than 3 years old [20]. In contrast to patients with OSA, these patients are less likely to be obese, have more orthostatic symptoms, and have low or normal BP [21].

Lastly, snoring without obstructive apneas, frequent arousals, or gas exchange abnormalities defines *primary snoring* [22]. Inherent in the definition, primary snoring is a diagnosis of exclusion requiring evaluation for other forms of SDB [14]. Historically, primary snoring was thought to be a benign condition, but studies do not always distinguish primary snoring from other forms of SDB [22]. One study made this distinction and excluded children with abnormalities on PSG other than snoring [23]. In this study, there were significant differences in neurobehavioral testing

Table 27.1 Sleep-disordered breathing: terms and definitions

SDB term	Definition
Obstructive apnea	Complete or partial upper airway obstruction with cessation in ventilation despite respiratory effort
Obstructive hypopnea	Decrease in airflow by at least 50 % despite effort
Apnea hypopnea index (respiratory disturbance index)	Total number of apneas and hypopneas per hour of sleep
Primary snoring	Snoring without abnormalities on PSG
Upper airway resistance syndrome	Partial upper airway obstruction causing arousals without gas exchange abnormalities
Obstructive hypoventilation	Partial upper airway obstruction resulting in hypercapnia
Obstructive sleep apnea	Obstructive apneas disrupting normal sleep patterns and normal ventilation during sleep

between children with primary snoring and children without snoring or SDB. Overall, both groups scored in the average range, but those with primary snoring scored significantly lower than the normal controls. This study suggests that primary snoring may not be benign and should be considered separately from other forms of SDB and normal controls. Table 27.1 summarizes the terms and definitions of the conditions that constitute SDB. Together, primary snoring, UARS, obstructive hypoventilation, and OSA represent the spectrum of SDB from mild to severe [20].

The prevalence of SDB in children is difficult to determine because of the heterogeneity in the studies assessing prevalence. Despite the availability of definitions and normative values for SDB, there is still no universal consensus on the criteria required for the diagnosis [14, 17]. In addition, most prevalence studies were based primarily on a variety of questionnaires, with few studies performing confirmatory diagnostic testing. Even when PSG was used in the study, the interpretation of the PSG scoring based on the AHI criterion used for diagnosis varied widely [24]. Lumeng and Chervin performed a systematic review of epidemiologic studies on SDB and, when applicable, performed a meta-analysis to adjust for the heterogeneity of results from the different studies [25]. They found the prevalence of snoring as reported by parents ranged from 1.5 % to 14.8 %, and the meta-analysis of relevant studies revealed a prevalence of almost 7.5 % [95 % confidence interval (CI), 5.75–9.61]. Parent-reported SDB ranged from around 4–11 %, and this range extended even further in both directions to 0.1–13 % when SDB was diagnosed by PSG and other diagnostic testing. However, a majority of the studies that used diagnostic testing reported a prevalence of OSA around 1–4 %. Recent American Academy of Pediatrics Clinical Practice Guidelines for the Diagnosis and Management of Childhood Obstructive Sleep Apnea Syndrome reported a prevalence of OSA syndrome of 1.2–5.7 % [24].

Clinical Presentation and Diagnosis

Snoring is the most common presenting symptom of SDB in children [18], but there is no correlation between the loudness or intensity of snoring and the severity of SDB [22]. Parents may also report the child having difficulty breathing while asleep or even witness apneas described as pauses in breathing usually followed by gasping, choking, or arousal [2]. Arousals may occur frequently without apneic spells manifesting as nighttime restlessness [26]. Parents may also observe paradoxical breathing movements representing continued attempts at respiration during upper airway obstruction. Other clinical features during sleep include sweating and posturing with a hyperextended neck to promote airway patency [20, 26]. A higher prevalence and association of nocturnal enuresis has been reported in children with SDB [27, 28] with improvement after adenotonsillectomy [29, 30]. Daytime symptoms may include morning headache, chronic mouth breathing, or behavior and attention problems resembling attention deficit hyperactivity disorder (ADHD) [14, 18]. Older children may also present with an ADHD symptoms, but they will more likely complain of daytime somnolence and fatigue, especially if obesity is also present [26].

Table 27.2 Clinical signs and symptoms

Snoring
Difficulty breathing while sleeping
Witnessed apneas
Paradoxical breathing movements
Arousals/restlessness
Sweating during sleep
Posturing to promote airway patency
Enuresis
Chronic mouth breathing
Morning headache
Behavior or attention problems
Daytime somnolence
Obesity
Adenotonsillar hypertrophy
Craniofacial disorders
Micrognathia/retrognathia

Physical exam findings for SDB include craniofacial disorders, retro/micrognathia, and obesity. The most common feature seen on physical exam is adenotonsillar hypertrophy, a finding more common in younger children because of the progressive increase in lymphoid tissue till about 12 years of age [2]. The degree of hypertrophy has been shown to correlate with the duration of obstructive apneas but not with the number of obstructive apneas [31]. Adenotonsillar hypertrophy may be less important in obese children. In a retrospective review of over 400 children with a mean age of 6.5 years and OSA, adenotonsillar size correlated with the AHI for nonobese children but not for obese children [32]. The obese group had a significantly higher Mallampati score than the nonobese group. The Mallampati score is based on how much the visual site of the soft palate, fauces, uvula, and tonsillar pillars is obscured with tongue protrusion. The higher the score, the more obscured the view, which suggests crowding of the upper airway even in the absence of adenotonsillar hypertrophy. The presence of any of these symptoms on history or physical exam should prompt further evaluation for SDB (Table 27.2).

Further evaluation for SDB typically includes referral to a sleep medicine clinic and/or a PSG. There have been many alternative diagnostic methods studied to confirm the presence of SDB without having to endure the burden and cost of a full overnight PSG in a sleep laboratory. Questionnaires are a good screening tool but cannot distinguish between primary snoring and OSA [26]. Audiotaping and/or videotaping may again screen for OSA and perhaps even detect apneas, but other abnormalities such as hypoventilation and hypopneas cannot accurately be detected without additional monitoring. Other techniques include continuous pulse oximetry recording and electrocardiography, but both techniques are limited because of technical application or lack of larger validation studies. Home monitoring studies have been used with some success proving to be both reproducible and valid in the context of a research protocol [33]. Regardless, no substitute has proven to be as sensitive and specific in diagnosing SDB as the gold standard, an overnight PSG in a sleep laboratory [22, 24, 34]. Initially, the respiratory indices and values used to diagnose OSA in adults were applied to children. However, because children have different physiology and respiratory rates than adults, guidelines for defining the various respiratory events were developed specifically for pediatrics [13]. Subsequently, normal values were published to aid in the interpretation of PSG in children [15], but the correlation of these values to adverse outcomes is not established [22]. Therefore, the diagnostic criteria and the classification for the severity of SDB are not consistent in the pediatric literature, making it difficult to compare multiple studies. Regardless, recent clinical guidelines from the American Academy of Pediatrics recommend screening for snoring and symptoms of SDB at every health maintenance visit followed by referral for a polysomnography for further evaluation [24]. Hypertension is included in the symptoms for SDB in these guidelines.

Pathophysiology

The pathophysiology of SDB in children is complex and not entirely understood, but the two primary abnormalities of the upper airway appear to be structural and functional. Structurally, when

measured endoscopically or noninvasively by pharyngometry or MRI, children with SDB have smaller cross-sectional areas and/or volumes of the upper airway than children without SDB [35–37]. On MRI, affected children were also found to have larger adenoids, tonsils, and soft palates [35]. Functionally, upper airway patency is maintained during sleep by neuromuscular responses to ventilation, oxygenation, and airway pressure [17, 38]. The neuromuscular response seems to wane with age. On a cross-sectional analysis of children and adults, the response to subatmospheric (negative) airway pressure decreased with increasing age and increasing body mass index (BMI) [39]. Therefore, children were able to maintain open airways at subatmospheric pressures better than adults, and a similar relationship was observed for BMI. As BMI increased, the response to subatmospheric airway pressure decreased. Additionally, when compared to controls, children with OSA had a decreased neuromuscular response to hypercapnia and intermittent, acute negative pressure during sleep [40]. Not only is the response affected during sleep, but Gozal et al. demonstrated more upper airway collapsibility during wakefulness in children with an AHI ≥5 [41]. The combination of narrower airways and increased susceptibility to upper airway collapse from a diminished neuromuscular response during sleep is a major contributing factor for the development of SDB in children.

The pathophysiologic mechanisms linking SDB and HTN are complex and multifactorial, with most available information coming from studies performed in adults. The autonomic nervous system plays a major role, but other factors have been identified, including vasoactive substances, endothelial dysfunction, and intrathoracic changes. Normally, during sleep, heart rate, BP, and sympathetic activity decline, but intermittent hypoxemia, hypercapnia, and arousals activate the sympathetic nervous system (SNS) [42, 43]. The surges in sympathetic activity during sleep result in increased BP and heart rate that can persist into wakefulness [44]. Vasoactive substances found to correlate with OSA in adults include endothelin [45] and aldosterone, although evidence of increased aldosterone has been limited to studies performed in adults with resistant HTN [9, 10]. Other vasoactive substances, including nitric oxide, are believed to contribute to endothelial dysfunction in adults. 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 [46]. There is evidence in children to suggest endothelial dysfunction in those with OSA and moderate to severe hypoxemia in whom significantly lower nitric oxide levels were measured [47].

Finally, the negative intrathoracic pressure created with sustained breathing efforts during upper airway obstruction may contribute to the autonomic responses during sleep in patients with OSA, leading to activation of the SNS and, ultimately, increased BP [43]. In addition to raising BP, the negative intrathoracic pressure may also have an effect on cardiac ventricular remodeling because of the transmural gradients created across the atria, ventricles, and aorta. Left ventricular transmembrane pressure is a reflection of the afterload on the left ventricle, and elevated left ventricular transmembrane pressures were detected during the ventilatory period following an obstructive apnea in adults with congestive heart failure [48]. This increase in cardiac afterload following obstructive apneas may explain the presence of left ventricular hypertrophy (LVH) in patients with OSA independent of BP [49].

Sleep-Disordered Breathing and Hypertension

Similar to the epidemiologic studies of SDB in children, studies evaluating the association of BP with SDB are heterogeneous and differ in the methods and criteria used to diagnose SDB and to measure BP. Some studies measured casual BP either with oscillometric devices [50, 51], calibrated sphygmomanometers [52], or mercury manometers [53]. One study monitored BP continuously using finger photoplethysmography [54]. The remaining studies measured ambulatory blood pressure (ABP) during wake and sleep [55–60] or only in relation to the PSG [61, 62].

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 in order to assess HTN status.

In regards to SDB, most studies divided participants into two or three groups depending on AHI or snoring, but one study only included patients with SDB [60]. Among the studies analyzing the association between BP and SDB ([Table 27.3]6.3), even with recent additions to the literature, there remains no clear consensus on how the two conditions relate. One of the earliest reports of HTN in the presence of SDB was a case series by Guilleminault et al. where five of the eight children with sleep apnea had HTN [63]. A later study assessing BP during PSG found children with OSA had significantly higher wake and sleep diastolic BP than those with primary snoring [62]. There was no difference in systolic BP between the two groups. However, when the groups were combined, both systolic and diastolic BP significantly correlated with the AHI. Recently, Weber et al. also compared similar groups (PS vs. SDB) but only found a difference in the sleep diastolic and mean BP [59].

Subsequent studies reported similar findings but also detected a difference in systolic BP among SDB groups [52, 57, 60, 61]. One study in Japan divided the participants into high AHI (AHI >= 10) and low AHI (AHI <10) groups and examined relationships between the AHI and BP during sleep [61]. A BP index was calculated by subtracting age-specific cutoff BP values designated as hypertensive in Japanese children from the subjects' mean measured sleep systolic and diastolic BP. Those with high AHI had a significantly increased systolic and diastolic BP index, but only the diastolic BP index correlated with the AHI. A more recent study evaluating the prevalence of hypertension among children with OSA demonstrated similar results [60]. The AHI correlated with the sleep systolic and diastolic BP and also with the wake diastolic BP obtained by ABP monitoring. Li et al. defined three SDB groups by AHI but excluded primary snorers [57]. Group 1 had an AHI <1; Group 2 had an AHI between 1 and 5; and Group 3 had an AHI >5. The mean BP levels in this study were converted to z-scores according to the LMS method described by Wuhl et al. [64]. There was no difference in the BP z-score between Groups 1 and 2, but Group 3 had a significantly higher wake and sleep systolic, diastolic, and mean arterial BP z-score than Groups 1 and 2. Furthermore, Group 3 had a significant association with wake systolic BP which was no longer significant after controlled for BMI. A similar study included primary snorers, mild OSA, and moderate/severe OSA compared to controls using continuous BP monitoring with finger photoplethysmography and consistently found an elevated mean arterial pressure and diastolic BP for wake and sleep for all three groups [54]. Only primary snorers had an elevated systolic BP for wake and sleep. When evaluating BP as a component of the metabolic syndrome in adolescents, Redline et al. also demonstrated patients with SDB (AHI ≥5) had significantly higher systolic and diastolic BP even after adjusting for age and BMI percentile [52].

Differences in diastolic BP have been less consistent in other studies [50, 55, 56, 58]. Leung et al. compared a high AHI (AHI ≥5) and a low AHI group (AHI <5) by 24 h ABP variables with a BP index defined as the measured BP divided by the 95th percentile for ABP [58]. This study also detected greater systolic and diastolic BP indices in the high AHI group, but the difference in diastolic BP was isolated to sleep measurements. Another study with the largest population to complete PSG did not find a difference in diastolic BP among the three study groups (no SDB, mild SDB, and moderate SDB) [50]. However, there was a significant increasing trend in the systolic and mean arterial BP across the groups. Furthermore, to delineate a threshold in AHI, the authors compared BP across SDB groups with incremental increases in AHI (i.e., AHI ≥1, AHI >≥2); the strongest association was between systolic BP and the group with an AHI ≥5. For this study, BP was not indexed to reference levels to account for the differences in age, gender, and height, and sleep BP was not measured.

Two studies failed to detect any differences in BP between participants with and without SDB. One study defined the groups by questionnaire

Table 27.3 Comparison of blood pressure studies

Source	SDB classification	Method of BP measurement	Method of BP analysis	Systolic BP results	Diastolic BP results	Mean arterial BP results	Nocturnal dip
Guilleminault et al. [63]	Case series of patients with OSA	NR	Presence or absence of HTN	NR	NR	NR	N/A
Marcus et al. [62]	OSA vs. primary snoring	Oscillometric during PSG	BP index	No difference	Elevated wake and sleep	NR	No difference
Kohyama et al. [61]	Low vs. high AHI	Oscillometric during PSG	BP index	Elevated wake and REMS	Elevated wake and REMS	NR	No difference
Li et al. [57]	Controls, mild, moderate SDB by AHI	ABPM	z-score	Elevated wake and sleep	Elevated wake and sleep	Elevated wake and sleep	No difference
Redline et al. [52]	SDB vs. no SDB	Aneroid manometer	Raw values	Elevated	Elevated	NR	N/A
Leung et al. [58]	Low vs. high AHI	ABPM	BP index	Elevated wake and sleep	Elevated sleep	NR	No difference
Bixler et al. [50]	Controls, mild, moderate SDB by AHI	Oscillometric	Raw values	Elevated	No difference	Elevated	N/A
Kaditis et al. [51]	Snorers vs. non-snorers by questionnaire	Oscillometric	Raw values	No difference	No difference	NR	N/A
Amin et al. [55]	Controls, mild, moderate SDB by AHI	ABPM	BP index and BP variability	No difference	Lower during wake	No difference	Linear trend across SDB groups
Amin et al. [56]	Controls, mild, moderate SDB by AHI	ABPM	Raw values	Elevated wake	Elevated wake and sleep	Elevated wake and sleep	NR
Enright et al. [53]	RDI	Mercury manometer	HTN vs. normal	HTN associated with RDI	HTN associated with RDI	NR	N/A
Reade et al. [73]	OSA vs. non-OSA	Manual BP	BP score	Elevated	Elevated	NR	N/A
Weber et al. [59]	OSA vs. primary snoring	ABPM	Raw values	No difference	Elevated sleep	Elevated sleep	Decreased for DBP and MBP
Horne et al. [54]	Controls, PS, mild, moderate SDB by AHI	Finger photoplethysmography	Raw values	Varied	Elevated wake and sleep	Elevated wake and sleep	N/A
Archbold et al. [65]	SDB vs. no SDB	Mercury manometer	Raw values	No difference	No difference	NR	N/A
Kirk et al. [60]	Only included cases with SDB	ABPM	Raw values/ hypertension vs. normotensive	Mean AHI correlated with sleep BP	Mean AHI correlated with sleep and wake	NR	NR

SDB sleep-disordered breathing, *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 monitoring, *DBP* diastolic BP, *MBP* mean BP, *PS* primary snorers

alone into habitual and non-habitual snorers [51]. The second study used PSG and casual BP measurements only when awake [65]. Amin et al. actually detected a lower diastolic BP in the group with the highest AHI [55]. This study defined three groups by AHI into primary snorers, mild SDB, and severe SDB. For this study, 24 h ABP was measured and BP index [(measured BP – 95th percentile)/95th percentile x 100] was compared across the three groups. Of all the BP variables including average wake and sleep systolic, diastolic, and mean arterial BP, only wake diastolic BP was significantly different among the three SDB groups with the lowest diastolic BP in the severe SDB group. The authors also analyzed BP variability defined as the average standard deviation of awake and sleep systolic, diastolic, and mean arterial BP. With this analysis, there was a dose-dependent increase in wake systolic and mean BP variability, as well as for all sleep BP, across the three groups. The authors proposed that variability in BP during both sleep and wakefulness suggests autonomic instability in children with SDB, resulting in BP dysregulation. The same group of authors later performed a separate but similar, more rigorous study and did detect significantly elevated BPs (except for sleep systolic BP) in those with a severe SDB compared to controls [56]. 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 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 [66–68]. The children in this study with severe SDB 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 is the first study evaluating the association of the morning surge with SDB in children, so further exploration of its implication in children is needed.

Despite the various studies reporting significant BP differences among a variety of SDB groups, none of the studies reported SDB groups with mean BP values consistent with HTN defined by a BP ≥95th percentile according to reference values for casual measurement [12] or for ambulatory measurements [64, 69]. Enright et al. dichotomized BP into HTN or normal [53]. In their study, the RDI was a significant predictor for systolic and/or diastolic HTN but HTN was defined as a BP ≥90th percentile for age, gender, and height [70]. Two of the previously mentioned studies defined HTN by 95th percentile. Leung et al. estimated HTN prevalence [58], defined as a mean wake, sleep, and/or total ABP ≥95th percentile for ABP reference values. They found the prevalence of HTN was significantly greater in the high AHI group. However, when the participants were combined regardless of AHI group, AHI was a significant predictor of HTN only when obesity was included in the model. Archbold et al. defined HTN by a casual BP ≥95th percentile for age, gender, and height [65]. Although the presence of SDB did not have an association with HTN, BP was significantly elevated in participants with SDB, and this elevation positively correlated with BMI and inversely correlated with total sleep time.

Obesity must be considered when evaluating the relationship between SDB and HTN since obesity is associated with both conditions [71, 72]. In the previous study by Li et al., BMI was found to be a confounding factor for wake systolic BP [57], i.e., the association was no longer significant when BMI was included in the model. However, the other previously mentioned studies that used PSG to determine SDB status found both BMI and SDB variables (i.e., AHI) to have an independent effect on BP [46, 50, 51, 55–58, 61, 62]. In one of the studies, SDB remained a significant predictor of BP when BMI was controlled for, but the effect of BMI on BP was not reported [52]. Yet another study, not previously mentioned, specifically addressed the interaction between SDB, BP, and obesity [73]. The objective was to assess if OSA was associated with an increased risk of HTN in obese children on a retrospective analysis of children who had undergone PSG, BP, and anthropometric measurement.

OSA was defined as an apnea index >1 or the lowest oxygen saturation associated with an obstructive apnea <90 %. A BP score was defined as the ratio of the measured BP to the 95th percentile for age, gender, and height [70], and BMI score was the ratio of measured BMI to the 95th percentile. Participants were classified and analyzed in three separate manners: (1) OSA versus non-OSA, (2) obese versus nonobese, and (3) obese hypertensives versus obese normotensives. For the three separate analyses, there was 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. Furthermore, on multiple regression analysis, the hypopnea index and BMI score were significant predictors for systolic and diastolic BP score in the OSA and obese groups. Among obese hypertensives, only BMI was significant for systolic BP score. All of these studies suggest there is an independent effect of BP and BMI on SDB. An interaction between BMI and SDB on BP also exists, but the causal relationship of this interaction and the effect on BP is yet to be elucidated.

Nocturnal Dipping

Nocturnal dipping refers to the normal physiologic decline in BP during sleep [74]. Normally, the mean nocturnal dip is 10–20 % lower than the mean daytime BP [75]. 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) [74]. The prevalence of non-dipping in adults with OSA is 48–84 % [8, 76, 77]. When compared to controls in one study, only patients with OSA were non-dippers, even though one of the controls had HTN. After controlling for several variables including age and BMI, only the RDI was a significant predictor of non-dipping status [77]. In children, the relationship between nocturnal dipping status and SDB has not been consistent [55, 57–59, 61, 62]. From the previously mentioned studies evaluating 24 h ABP, most do not show a statistically significant difference in the proportion of non-dippers among children with SDB compared to those without SDB [57, 58, 61, 62]. Two of the studies demonstrated a higher proportion of non-dippers in the SDB group compared to the group without SDB (29 % vs. 19 % and 12 % vs. 4 %, respectively), but the difference was not statistically significant [61, 62].

Rather than comparing the proportion of non-dippers, other studies have examined the mean nocturnal dip according to SDB, either in multiple groups defined by AHI [55, 57] or according to the presence or absence of SDB [59]. In the first study, the average nocturnal dip per group significantly decreased for systolic, diastolic, and mean arterial BP across the three groups [55]. The proportion of non-dippers per group was not reported, but the mean nocturnal dip was blunted (<10 %) for systolic BP in both groups with an AHI >1. In the second study, there was no difference in the mean nocturnal dip nor the proportion of non-dippers per group [57]. The third and final 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 [59]. The inability to consistently demonstrate significant differences in the nocturnal dip among SDB groups is likely another result of the heterogeneity among studies. Regardless, a child or adolescent undergoing evaluation for elevated BP with an abnormal nocturnal dip on ABP monitoring warrants further screening and/or evaluation for SDB, especially in the presence of other risk factors.

Left Ventricular Geometry

In children and adolescents with systemic HTN, LVH is recognized as the most common surrogate marker of end organ damage [12]. In adults with OSA, the intermittent obstructive apneas lead to increased afterload [48], possibly contributing to the development of LVH. Therefore, patients with both HTN and OSA may have an even greater risk of LVH. Adult data suggests LVH is independently associated with OSA [49, 78]. One of the first studies addressing left ventricular geometry and SDB 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 [79]. Furthermore, AHI was the only significant predictor of LVMI. Participants with an AHI >10 were about 11 times more likely to have LVH independent of age, gender, and BMI (resting BP was not included in the final model because it was not a significant predictor of LVMI). This dose-dependent effect of the severity of SDB on LVMI was consistent in a later report from the same group with additional participants [80]. A separate study from the same group with different participants measured ABP in addition to resting BP and divided the study population into three SDB groups according to AHI severity (controls, moderate SDB, and severe SDB) [56]. There was a progressive, but insignificant, increase in LVMI across the three groups as AHI worsened. There was a difference in left ventricular relative wall thickness between controls and the severe SDB group, and all BP parameters (wake and sleep systolic, diastolic, and mean arterial BP) were significant predictors for this relationship. One additional study evaluated echocardiographic parameters in adolescents with SDB compared to controls and found a correlation between the RDI and left ventricular posterior wall thickness, but LVMI was similar in the two groups [81]. The most recent study including echocardiography found LVM was normal for all participants, even for the few detected to have HTN [60]. Although some evidence suggests that LVMI increases with worsening AHI, there has not been a clear, independent association demonstrated between LVH and SDB in children and adolescents.

Treatment

Adenotonsillectomy is the recommended first-line treatment for OSA in children [24]. Other surgical treatment options include uvulopalatoplasty, nasal surgery, maxillofacial surgery, or even in extreme cases tracheotomy, but these are rarely necessary [17]. For those who are not surgical candidates or fail to have a response to surgery, continuous positive airway pressure (CPAP) is a nonsurgical alternative [22, 24]. CPAP is fairly well tolerated in children, but compliance is necessary and can be poor secondary to minor side effects such as rhinorrhea, nasal congestion, or dryness [2]. Alternatively, intranasal steroids are recommended for nonsurgical candidates or those with mild postsurgical OSA (AHI <5); however, the long-term use and effectiveness of intranasal steroids is unknown [24]. Study participants have shown a significant improvement in the AHI and in behavioral and cognitive symptoms after treatment of SDB [82, 83], and some studies have even shown an improvement in left ventricular geometry and/or function [80, 84]. For example, one of the previously mentioned studies by Amin et al. compared pretreatment and posttreatment left ventricular diastolic function by mitral inflow velocity [80]. Treatment for SDB either consisted of adenotonsillectomy +/− uvulopalatoplasty or CPAP. Pretreatment there was a progressive decline in diastolic function across the SDB groups correlating with increasing severity. Posttreatment, regardless of therapy, the SDB groups had an improvement in diastolic function to a level similar to controls (primary snorers). Another study reported significant baseline differences between the SDB and control groups in regards to left ventricular measures and compliance, but after adenotonsillectomy, measurements in the SDB group were no longer different from controls [84].

Few studies have reported the treatment effect of SDB on BP in children. In the aforementioned case series by Guilleminault et al., five of the eight patients with OSA had HTN at presentation [63]. Those who underwent adenotonsillectomy and demonstrated improvement of symptoms on follow-up PSG were no longer hypertensive. Two patients with HTN had extreme cases of OSA and required tracheotomy. Both cases also showed significant improvement in SDB symptoms and resolution of HTN after surgery. Two studies have specifically evaluated the effect of adenotonsillectomy on BP in children [85, 86]. The first study used casual BP measurements [85]. Children with complete resolution of SDB after surgery (AHI <1) had a significant decrease in diastolic BP but not in systolic BP. The second study, which utilized ABPM, found that the 24 h

diastolic ABP load was reduced after surgery [86]. A subgroup analysis of those with HTN prior to surgery demonstrated an improvement in sleep BP loads for both systolic and diastolic BP.

Although an association between drug-resistant HTN and OSA has been described in adults [7, 8], there are currently no similar reports in children. However, in a child with risk factors for SDB and difficult to control HTN, the presence of SDB should be considered.

Conclusions

Despite the heterogeneity and conflicting data, the studies in children and adolescents suggest that a relationship exists between elevated BP/BP variability and SDB. This relationship is significantly independent of obesity, but obesity also has an independent association with SDB and with HTN [71, 72]. How the three conditions interact and whether there is a causal relationship among the conditions is unknown and requires further investigation. Furthermore, changes in left ventricular structure and function have been found to occur in childhood. Similar to obesity, these left ventricular changes are associated with both HTN and SDB, and after treatment of SDB alone, the changes improve. Therefore, the evaluation of a child with HTN should identify clinical signs and symptoms of SDB during the history and physical exam. Snoring and adenotonsillar hypertrophy are the two most common risk factors for SDB in children, and the presence of either sign in a child with HTN warrants further evaluation for SDB, especially in the presence of obesity.

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Hypertension in the Pregnant Teenager

28

Tracy E. Hunley, Neerav Desai, and Deborah P. Jones

Abstract

Hypertension occurs in approximately 15–20 % 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 orders 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 • Preeclampsia superimposed upon chronic hypertension • ABPM • Preterm birth • Adolescence • Placental ischemia

Abbreviations

2-ME	2-methoxyestradiol
ABPM	Ambulatory blood pressure monitoring
ACEi	Angiotensin-converting enzyme inhibitors
ANP	Atrial natriuretic protein
ARB	Angiotensin receptor blocker
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
COMT	Catechol-O-methyltransferase

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DBP	Diastolic BP
GFR	Glomerular filtration rate
HELLP	Hemolysis, elevated liver enzymes, low platelets syndrome
HIF	Hypoxia-inducible factor-1
MAP	Mean arterial pressure
OR	Odds ratio
PlGF	Placental growth factor
SBP	Systolic BP
sEng	Endoglin
sFlt1	Soluble fms-like tyrosine kinase 1
VEGF	Vascular endothelial growth factor

Introduction

About 15–20 % of pregnancies are complicated by hypertension, which may lead to 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 [1, 2]. Preexisting chronic hypertension and obesity can increase both the risk for worsening hypertension during pregnancy (including preeclampsia) and higher rates of preterm birth and fetal growth insufficiency.

Blood pressure (BP) levels during the first half of pregnancy are lower than before pregnancy, a physiological change that challenges the clinician in the choice of BP thresholds in 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 orders in pregnancy, normal blood pressure (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 (normal, <0.2). Her follow-up to the 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 taking an angiotensin receptor blocker (ARB)?

The Pregnant Adolescent: General Considerations

Adolescent pregnancy is a significant burden across the world with an estimated 14 million children born to women between 15 and 19 years of age [3]. The United States has one of the highest rates among developed countries, with almost 750,000 teens becoming pregnant every year [4]. It is estimated that up to two-thirds of adolescent pregnancies in the United States are unplanned [5].

Approximately two-thirds of teenage pregnancies result in live birth and one-third end in abortion [4]. There is considerable variation among regions of the United States with the 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 whites in the United States. Finally, lower socioeconomic status and lower levels of parental education also have strong correlations with teenage pregnancy [6]. 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 [7–9].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 [10].

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 [11]. 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 caretaking responsibilities, personal health and nutrition, finances, and educational or vocational responsibilities [12]. 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 [13]. 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 [14]. 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 [14].

Pregnant adolescents require additional resources and specialized care, so clinicians can utilize existing relationships among the teen and her family, peers, and partners. The initial reaction of the pregnant teen may be to conceal her pregnancy from family members and/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 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 the 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 [2].

Table 28.1 Classification of hypertensive disorders of pregnancy

<20 gestational weeks	≥ 20 gestational weeks	≥ 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

Adapted from Garovic [78]
HTN hypertension

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) [1]: preeclampsia, chronic hypertension, preeclampsia superimposed upon chronic hypertension, and gestational hypertension (Table 28.1). The term pregnancy-induced hypertension which is not included in the classification scheme shown in Table 28.1 has been used in some studies and publications; the use of this term is discouraged because it might refer to either gestational hypertension or preeclampsia.

Chronic hypertension is defined as SBP≥140 and/or DBP≥90 before pregnancy or before 20 weeks gestation. It is possible that chronic hypertension may be initially designated as gestational hypertension with delay in 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. The degree of BP elevation during pregnancy has also been included as an additional criterion (see next section on pattern of BP during pregnancy): Systolic BP (SBP) and diastolic BP (DBP) increases of ≥30 mmHg and ≥15 mmHg, respectively, when accompanied by proteinuria and/or hyperuricemia. Such conditions may warrant increased monitoring even if the BP does not exceed the threshold limits of 140/90.

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 ≥300 mg per 24 h, by urine protein/creatinine ratio (Upc) >0.3, or if those methods are not available, then ≥1+ by dipstick on at least two random urine samples collected more than 6 h apart [15]. A random urine protein/creatinine ratio is not recommended by experts to be used in place of the timed urine collection. The correlation between 24 h urine protein and Upc was moderate ($R^2=0.41$), and a Upc<0.3 had a negative predictive value of 47.5 % among women with suspected preeclampsia [16]. Similarly, Upc did not perform well in predicting significant proteinuria in gestational hypertension [17]. While proteinuria has been classically 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.

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 with hypertension secondary to renal parenchymal disease, such as the illustrative case, detection of preeclampsia may be challenged by preconception proteinuria. Furthermore, chronic hypertension is a significant risk for development of preeclampsia. The onset of proteinuria or marked worsening of proteinuria, marked worsening of 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. The latter definitions would not be applied until completion of pregnancy (if preeclampsia did not develop). 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.

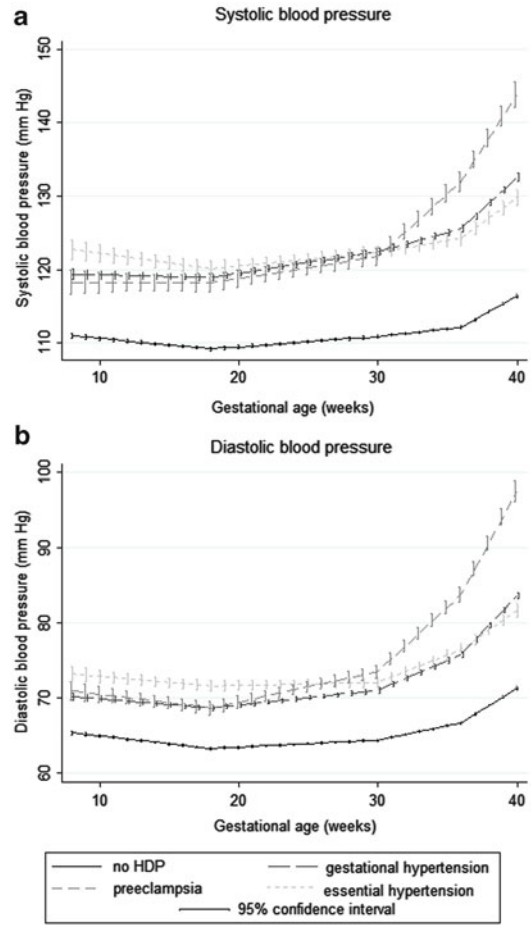


Fig. 28.1 Average trajectories of systolic and diastolic blood pressures by hypertensive disorders of pregnancy in the unadjusted joint model (N = 13016) (From Macdonald-Wallis et al. [18])

BP Patterns Through the Course of Pregnancy

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 [2]. Clinical 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 [18]. 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. 28.1). 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. 28.1). 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.

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 value of ambulatory BP levels in predicting preeclampsia and pregnancy-induced hypertension [19, 20]. There were significant differences in both casual and ambulatory 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. At 28 weeks, there were significant differences in ambulatory SBP and DBP; 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 with the highest quartile of BP had the highest incidence of preeclampsia [19]. 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 and night mean BP. Despite significantly different mean BP levels in both hypertensive groups as compared to the normal group, ambulatory BP levels performed poorly in predicting who would develop gestational hypertension or preeclampsia [20].

The pattern of ambulatory BP throughout pregnancy has been extensively characterized by Ramón Hermida and coworkers, who have argued that use of casual 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 casual BP levels misclassify individuals at risk. Pregnant women with masked gestational hypertension (high ambulatory and normal clinical BP) have comparable outcomes (preterm delivery and IUGR) as those with both abnormal ambulatory and casual BP [21]. Differences in mean 24-h BP levels were noted toward the end of the first trimester; those who developed gestational hypertension had an ambulatory BP of 115/67 as compared to normotensive women whose mean BP was 103/60. Ambulatory BP data from normotensive pregnant women throughout gestation generated rest-activity-specific reference thresholds. From these, a hyperbaric index is calculated; abnormal BP elevation was defined as greater than 15 mmHg/h [22]. As illustrated in Fig. 28.2, ambulatory BP 90th percentile threshold levels are lower in the normal pregnant female as compared to the normal nonpregnant female. The use of ambulatory BP monitoring and specifically of the hyperbaric index, which does not lend itself to clinical practice, has not been widely adapted for characterization of BP during pregnancy.

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 [23]. In so doing, cytotrophoblast

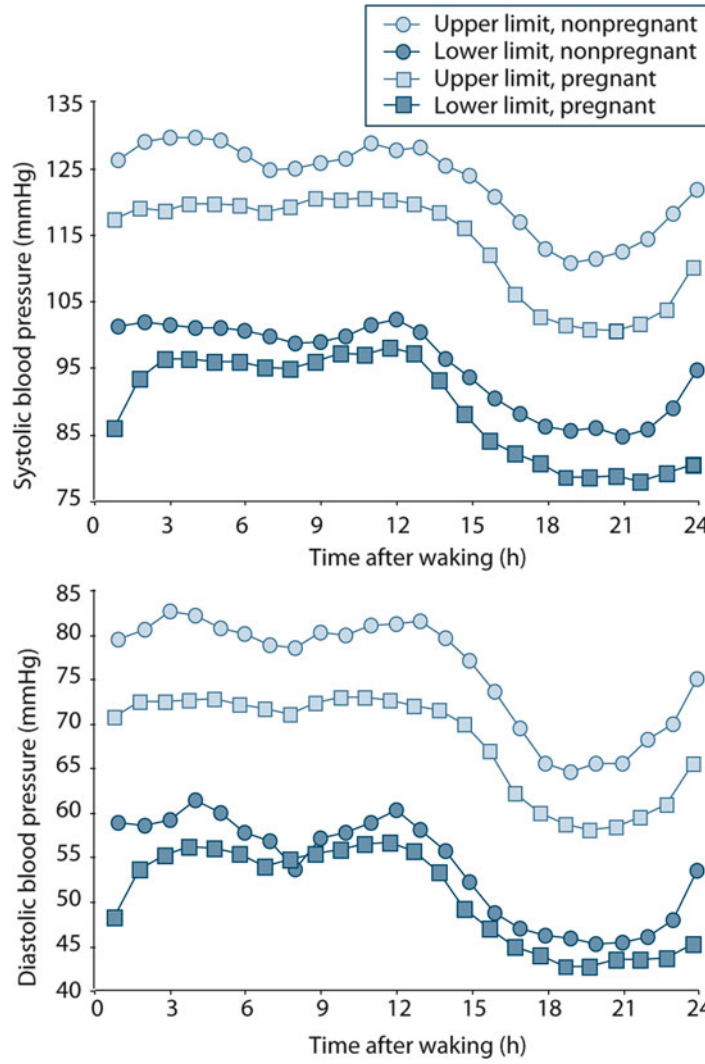


Fig. 28.2 Circadian 90 % tolerance intervals for systolic and diastolic blood pressure. From a reference population of normotensive nonpregnant and normotensive pregnant women who were assessed by 48-h ambulatory monitoring in the second trimester of pregnancy (From Hermida and Ayala [84])

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 placentas from non-preeclamptic pregnancies (range, 76–100 %) [24]. 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 >4,000 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) [25]. 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

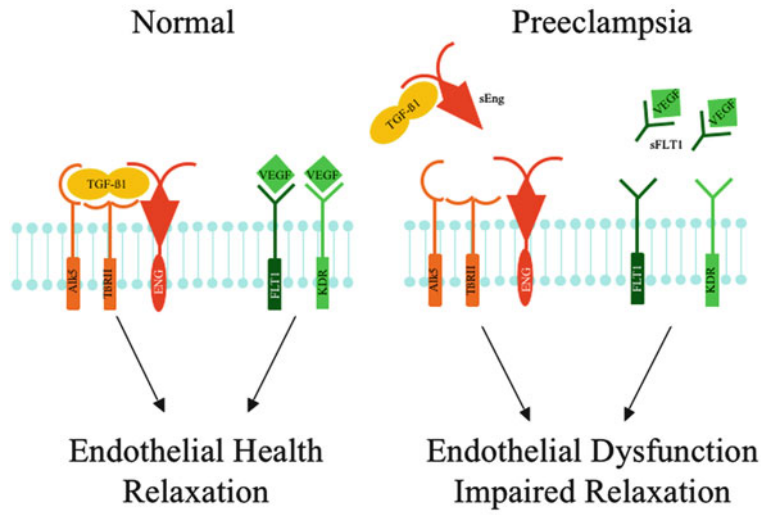


Fig. 28.3 Soluble fms-like tyrosine kinase 1 (sFlt1) and soluble endoglin (sEng) cause endothelial dysfunction by antagonizing vascular endothelial growth factor and transforming growth factor-β1 (TGF-β1) signaling. VEGF and TGF-β1 maintain endothelial health. During normal pregnancy, vascular homeostasis is maintained by physiological levels of VEGF and TGF-β1 signaling in the vasculature; however, in preeclampsia, excess placental secretion of sFlt1 and sEng, which are endogenous anti-angiogenic protein, inhibits VEGF and TGF-β1 signaling in the vasculature, resulting in endothelial dysfunction and the accompanying decreased prostacyclin and nitric oxide production as well as release of procoagulant proteins. TβRII indicates TGF-β1receptor (From Powe et al. [23])

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. Moreover, two human corin mutations which markedly reduce enzymatic activity were identified in preeclamptic women [26].

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 [27, 28]. 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, and 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 toward vasoconstriction.

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 preeclamptic mothers. 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. Deprived of normal VEGF signal (such as podocyte to endothelial VEGF signaling in glomerular capillaries), maternal endothelium becomes dysfunctional (Fig. 28.3). Normally, 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 [29, 30], while the VEGF Flt1 receptor also contributes to endothelial permeability and survival [31]. 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 [32]. 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 [33].

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 [34]. 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 (50–1,000 pg/ml); circulating VEGF represents a small fraction as the majority VEGF is membrane bound. Further linking sFlt1 in the pathophysiology of preeclampsia are observations that its placental expression and maternal circulating level are augmented by hypoxia/hypoperfusion [28, 35]. Lastly, utilizing apheresis with a dextran sulfate cellulose column, reduction of elevated circulating sFlt1 level in severe preterm preeclamptic women was accompanied by reduction in BP and proteinuria as well as prolongation of pregnancy for 2–3 weeks [36].

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 which contributes to normal vascular functioning including vasodilatation through nitric oxide [37]. 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 [37]. In preeclamptic mothers, reduction in circulating nitrite (metabolic by-product of nitric oxide metabolism) correlated with elevations in sEng (as well as sFlt1) [38].

Effects of sEng and sFlt1 appear synergistic. Thus, while experimental infusion of sFlt1 causes hypertension and proteinuria, co-infusion 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) [37]. 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) [39].

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 [40]. 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 [41]. COMT null mutant mice, absent 2-ME, have elevated HIF and sFlt1 and preeclampsia, all ameliorated by exogenous 2-ME administration [42]. 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 [43, 44].

Autoantibodies to the angiotensin AT1 receptor (AT1-AA) have been detected in the serum of preeclamptic women; these antibodies function as receptor agonists. Increased receptor activity might explain the exaggerated pressor response to angiotensin II observed in preeclamptic compared with normal pregnancies [45]. 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 [46]. Importantly, AT1-AA recovered from patients with preeclampsia produced preeclampsia when administered to pregnant mice [47]. Whether these effects are directly AT1 related or AT1 mediated through AT1-AA induction of sFlt1 and sEng is not clear [48].

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 [34]. 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) [49]. 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 [50]. Women with gestational hypertension demonstrate a reduction in circulating nitrite (reflecting reduced endothelial nitric oxide) though to a lesser degree than preeclampsia [49]. 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 [51]. Even AT1-AA levels were intermediate in patients with gestational hypertension between those with preeclampsia (higher) and normotensive pregnancies (low) [52]. Though not a universal view, these observations speak to diffuse endothelial dysfunction underlying both gestational hypertension and preeclampsia, differing mainly by degree [53].

Table 28.2 Risk factors for preeclampsia with relative risk (95 % confidence intervals)

Risk factor	Relative risk (95 % confidence intervals)
Nulliparity	2.91 (1.28–6.61)
Previous preeclampsia	7.19 (5.85–8.83)
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 ≥ 130 mmHg at first evaluation	2.37 (1.78–3.15)
DBP ≥ 80 mmHg at first evaluation	1.38 (1.01–1.87)
Preexisting DM	3.56 (2.54–4.99)
Preexisting HTN	Increased risk[a]
Preexisting renal disease	Increased risk

Note: Maternal age ≤ 16, 17, or 19 years not associated with increased risk for preeclampsia

Adapted from Duckitt and Harrington [54], Steegers et al. [85]

BMI body mass index, *DBP* diastolic blood pressure, *DM* diabetes mellitus, *HTN* hypertension, *SBP* systolic blood pressure

[a]Odds ratio 1.6 (1.1–2.2) from Sibai et al. [66]

Risk Factors for Preeclampsia

Risk factors for preeclampsia are listed in Table 28.2. 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 risk of 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 [54]. 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 [55]. There was a pattern of consistently higher

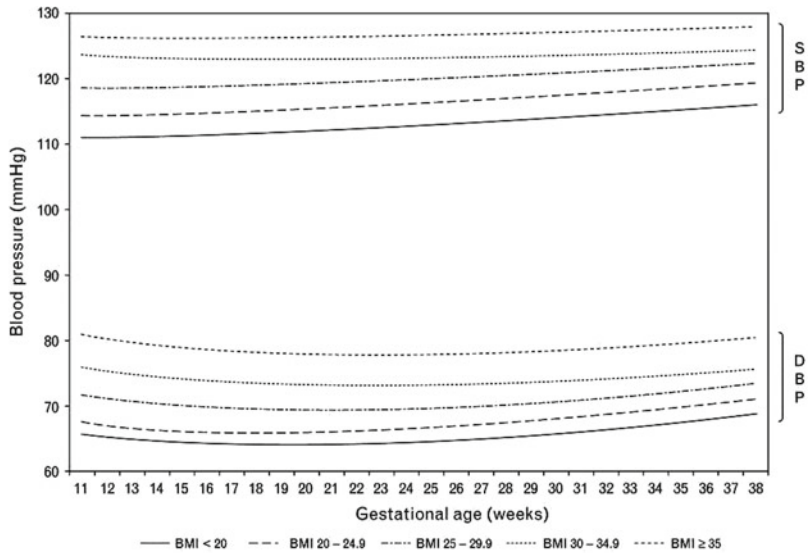
SBP and DBP for higher BMI throughout pregnancy (Fig. 28.3). The odds ratios for gestational hypertension (the term pregnancy-induced hypertension was used) for the overweight/obese/morbidly obese groups as compared to the group with normal BMI were 2.12 (CI 1.54–2.91), 4.67 (3.07–7.09), and 11.34 (6.80–18.86) and for preeclampsia were 1.82 (CI 1.16–2.83), 2.49 (CI 1.29–4.78), and 3.40 (1.39–8.28), respectively [55]. Additionally, the 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.

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 pregnancy and particularly 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 (casual BP at or above the 95th percentile for age and height percentile). An SBP threshold of 140 mmHg is greater than the 99th percentile for females 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 hypertension, BP levels in teenagers were compared to those of adult women: SBP was 133.4 ± 15 mmHg at the beginning of monitoring for the teenage group and 139.5 ± 15 mmHg for the adult group. Similarly, DBP levels were lower in the teenagers, 84.1 ± 13.6 mmHg versus 90.1 ± 11.5 mmHg in the adults [56]. A small retrospective study among mothers 15–19 years of age found that the second trimester MAP >80 mmHg (in contrast to a threshold MAP of 90 mmHg used for adult women) had an sensitivity of 60 % and specificity of 93 % in predicting gestational hypertension, with a positive predictive value of 76 % and negative predictive value of 82 % [57].

Earlier studies reported a higher incidence of hypertension (preeclampsia/eclampsia) among younger mothers [58, 59]; however, this has been disputed by more recent epidemiologic studies, including a meta-analysis [54, 60–62]. There was a lower incidence of hypertension in teenage mothers (mean age 18.3, range 13.7–19.9y) as compared to mothers 20–35 years of age (3.7 % vs. 6.6 %) [62]. 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 8,000 primiparous women at the University Hospital of Caen, France [61]. A systematic review of controlled cohort studies examined the risk of preeclampsia according to maternal age and concluded that younger maternal age was not a significant risk factor [54].

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 35 kg/m^2), overweight (BMI 25–29.9 kg/m^2), obese (BMI 30–34.9 kg/m^2), and morbidly obese (BMI > 35 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 kg/m^2 [63]. This emphasizes the multiple levels of risk associated with the overweight/obese adolescent with respect to pregnancy-associated hypertension: not only they are at risk for primary hypertension, but they are also at increased risk for pregnancy-related hypertension due to higher BP levels and BMI (Fig. 28.4).



Blood pressure patterns in different prepregnancy BMI categories. Change in SBP and DBP in mmHg for lean, overweight, obese and morbidly obese women, compared to women with a normal BMI based on repeated measurement analysis. SBP = $\beta_0 + \beta_1 \times$ BMI + $\beta_2 \times$ gestational age + $\beta_3 \times$ gestational age^{-2} + $\beta_4 \times$ BMI × gestational age. DBP = $\beta_0 + \beta_1 \times$ BMI + $\beta_2 \times$ gestational age + $\beta_3 \times$ gestational age$^{0.5}$ + $\beta_4 \times$ BMI × gestational age. In these models, '$\beta_0 + \beta_1 \times$ BMI' reflects the intercept and '$\beta_2 \times$ gestational age + $\beta_3 \times$ gestational age^{-2}' reflects the slope of change in blood pressure per week for SBP, and '$\beta_2 \times$ gestational age + $\beta_3 \times$ gestational age$^{0.5}$' reflects the slope of change in blood pressure per week for DBP. Our term of interest is β_4, which reflects the difference in change in blood pressure per week per BMI category, as compared to women with a normal BMI, 20–24.9 kg/m^2. Estimates and *P* values are given in Supplementary Table S1, http://links.lww.com/HJH/A80.

Fig. 28.4 Blood pressure patterns in different prepregnancy BMI categories (From Gaillard et al. [55])

Impact of Chronic Hypertension on Pregnancy Outcome

The prevalence of chronic hypertension among females of childbearing 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 [64]. Females with chronic hypertension who become pregnant are at increased risk for developing preeclampsia and of developing preeclampsia relatively earlier in gestation [65]. Preeclampsia occurred in 10–25 % of women with mild chronic hypertension with an average across the four available studies of 20.8 %. 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 [65, 66]. Chronic hypertension 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 [65]. 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 [66]. Proteinuria in the setting of chronic hypertension prior to pregnancy is a risk factor for preeclampsia and/or fetal growth restriction [66]. It has been recommended that risk be assigned to women with chronic hypertension who become pregnant. Women considered to have low risk 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 [67]. The case illustrates this concept – an existing diagnosis of chronic, severe hypertension with baseline proteinuria is associated with marked 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 are 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 hypertension 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 ARBs.

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 the last menstrual period and then stratify the young women based on other risk factors. A thorough history of chronic disease such as hypertension, diabetes, thyroid disease, or other long-standing systemic diseases should also be elicited. In addition to placing the mother on a prenatal vitamin, the provider should document all medications and herbal supplements and then determine if they pose a risk to the mother or fetus. We also assess each patient for certain parameters including nutrition 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 of contraceptive methods in conjunction with potential harm from antihypertensive medications [68]. 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 adjunct.

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 [69]. 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 [65]. The American College of Obstetricians and Gynecologists recommends initiation of antihypertensive therapy if the SBP is ≥180 mmHg and/or DBP ≥ 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 [65]. In contrast, the European Society of Hypertension/European Society of Cardiology guidelines recommend initiation of antihypertensive medication for BP 140/90 or greater [70].

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/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 challenging because of a paucity of information regarding safety and efficacy of specific agents during pregnancy. The most commonly used antihypertensive drugs during pregnancy include methyldopa, labetalol, hydralazine, metoprolol, extended release nifedipine, and hydrochlorothiazide [65]. Methyldopa 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; however, no difference in the risk for development of preeclampsia/eclampsia was found [71]. Recommendations from a recent review article include the following two proposals [70]: (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 methyldopa and hydralazine).

Treatment of hypertension reduces maternal morbidity but has no proven effect on fetal outcomes. Treatment to lower maternal blood pressure was not associated with differences between treatment and placebo on fetal outcomes such as preterm birth, intrauterine growth restriction, or fetal death [71]. The effect of beta-blockers (vs. placebo, or an agent other than beta-blocker) on the incidence of small-for-gestational-age infants, an analysis including 12 trials reported a summary relative risk of 1.36 (1.02–1.82) [72]. 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 [72]. 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 g [73]. 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 [70]. Since chronic hypertension is associated with significant morbidity for the mother and her baby, one could argue that treatment would be beneficial for both.

As mentioned earlier, ACEi and ARBs should never be used during pregnancy; they increase the risk for fetal developmental abnormalities [74]. The term fetal renin-angiotensin system blockage syndrome (fetal RAS blockade syndrome) was recognized in the early 1980s as a result of intrauterine exposure to ACEi. 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 an 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) [74]. A systemic review of ACEi and ARB exposure reported the prevalence of fetal RAS blockade syndrome by trimester and duration of exposure [75]. ARB exposure had a higher prevalence of neonatal complications (87 %) as compared to ACEi exposure (48 %). Risk for fetal RAS blockade syndrome was lowest for isolated first trimester exposure as compared to exposure during the second and/or third trimesters. There are

conflicting studies – not all support the findings of the previously cited study; this is a controversial topic which was recently extensively reviewed [76]. Other studies have found no increased risk for fetal malformations to be associated with first trimester exposure to ACEi as compared to babies born to mothers with untreated gestational hypertension or mothers with other antihypertensive medications [77].

Detection of pregnancy in the teenager with preexisting hypertension should prompt immediate discontinuation of ACEi and ARBs due to their potential fetal effects. In fact, many argue that use of these agents should be avoided in females of childbearing potential who are not using a reliable method of contraception. There are no objective guidelines to indicate that pregnancies in which there is ACEi/ARB exposure should be terminated. Given that the majority of infants with first trimester (when termination is most likely to be considered) ACEi/ARB exposure do not have serious sequelae, counseling regarding the options for termination of pregnancy would not necessarily be different than for that of any other pregnancy.

Risk of Future Cardiovascular Disease and Renal Disease

The presence of hypertension during pregnancy increases the woman's and her offspring's future risk of developing cardiovascular disease. 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 [78]. 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 cardiovascular disease, diabetes mellitus, smoking, and dyslipidemia [79]. 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 cardiovascular disease in general, it is unclear whether the association of gestational hypertension and future cardiovascular risk is causal or due to common etiologies. It has been suggested that pregnancy serves as a physiological "stress test" or "screening test" which unmasks underlying metabolic perturbations and endothelial dysfunction [80].

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 [81]. Mean BP measured using a mercury sphygmomanometer in the hypertensive group during the mid-third trimester was 121.4 ± 1.2/78.8 ± 0.9 mmHg compared to 112 ± 1.1/69.5 ± .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 ± 2.4/78.3 ± 1.6 mmHg) versus the normal group (117.1 ± 1.2/73.4 ± 1.3 mmHg). Offspring of the gestational hypertensive mothers had higher mean SBP compared to those with normal maternal BP: 97.6 ± 1.3 versus 93.1 ± 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 [81]. 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/m2 after exposure to preeclampsia [82]. 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 [83]. 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 event as adults.

Conclusions

Hypertensive disorders of pregnancy represent a major cause of maternal deaths in the United States as well as 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 cardiovascular disease 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 develop 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 blood pressure levels after initiation of therapy.

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Sequelae of Hypertension in Children and Adolescents

29

Donald J. Weaver Jr. and Mark M. Mitsnefes

Abstract

Hypertension is a well-characterized risk factor for the development of cardiovascular, cerebrovascular, and renal disease in adults. More recently, data obtained from autopsy studies as well as noninvasive imaging techniques have demonstrated that similar end-organ changes occur in children and adolescents with mild to moderate elevations in blood pressure. Specifically, chronic elevations in blood pressure in pediatric patients lead to changes in left atrial as well as left ventricular structure. These 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. Recent studies have highlighted the impact of mild to moderate elevations in blood pressure on 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

Hypertension is a significant public health challenge because of its high prevalence as well as its associated complications, including cerebrovascular disease, renal failure, and heart failure [1]. In fact, hypertension is the second leading cause of end-stage renal disease (ESRD) among adults in the United States [2]. Moreover, hypertension

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is the leading risk factor for cardiovascular mortality and ranked third as a cause of disability-adjusted life years in adults [1, 3]. A recent study examining the economic burden of chronic cardiovascular disease suggested that medical expenditures attributable to hypertension are estimated at more than 73 billion dollars annually [4]. More disturbing is the fact that hypertension has its origins in childhood, and hypertension in children is a risk factor for development of adult cardiovascular disease [5, 6]. However, hypertension in children is often underdiagnosed, and the alterations in end-organ structure and function noted in adult hypertensive patients likely also have their origins in childhood [7, 8]. Since treatment of hypertension has been shown to improve cardiovascular outcomes and to reduce the risk for development of these complications in the adult population, we hypothesize that prompt recognition of these alterations in children and adolescents may also prevent future morbidity and mortality in pediatric patients [9].

Primary hypertension in children and adolescents is generally thought to be an asymptomatic disease not associated with emergent adverse events. However, even in the early stages of hypertension, children and adolescents experience nonspecific symptoms that can impact school performance. Croix and Feig [10] reported that 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 [10]. More strikingly, treatment of hypertension significantly reduced the prevalence of these complaints 6 months following initiation of therapy, highlighting the importance of screening and recognition of early hypertension [10]. In addition to the symptoms described above that affect quality of life and school performance, childhood hypertension leads to abnormalities in several organ systems with the potential for significant long-term morbidity as outlined below (Table 29.1).

Table 29.1 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 LV failure is preceded by alterations in both left atrial and left ventricular geometry [11–13]. The changes in ventricular geometry occur in two different patterns [13]. In concentric LV hypertrophy, parallel addition of sarcomeres causes an increase in the cross-sectional area and diameter of the cardiac myocytes [14]. These alterations lead to a significant increase in LV wall thickness out of proportion to an increase in size of the LV cavity [14]. In contrast, asymmetric increase in wall thickness as well as LV cavity size results in eccentric LVH as a result of sarcomere addition in series. Hypertension is generally associated with development of concentric hypertrophy as increased blood pressure and pulse pressure oppose LV ejection inducing increased LV wall stress [15]. In addition to left ventricular stress, numerous nonhemodynamic factors are thought to influence the development of altered left

ventricular geometry, including neurohormonal activation, biomarkers of inflammation, and hemostatic factors [16–20]. Recently, a central role for the renin–angiotensin–aldosterone system (RAAS) was proposed based on a cross-sectional study examining the contribution of several biomarkers including C-reactive protein, plasminogen activator inhibitor-1, B-type natriuretic peptide, renin, and aldosterone [21]. The investigators found that the aldosterone–renin ratio alone was significantly associated with development of both concentric and eccentric remodeling [21]. 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 [16]. 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 [16]. Furthermore, abnormalities in myocardial electrical conduction in the hypertrophied muscle may also trigger the development of arrhythmias.

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 [22]. However, only age, race, and obesity were significant predictors of left atrial size in hypertensive adults [23]. While not consistently associated with hypertension, the presence of left atrial enlargement is significant because it is associated with development of cardiac arrhythmias, cerebrovascular events, and death in hypertensive adults [24]. Although data are limited in the pediatric population, Daniels et al. [25] studied a cohort of 112 pediatric patients with hypertension and found that 51 % of the patients had left atrial dimensions above the 95 % upper confidence limit. In their analysis, height, body mass index, and systolic blood pressure were independent predictors for left atrial enlargement [25]. Interestingly, left ventricular geometry was also an independent predictor of left atrial size, and children with eccentric left ventricular hypertrophy demonstrated increased left atrial size compared to patients with other forms of left ventricular geometry [25]. 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 [25]. The prognostic value of these findings in pediatric patients remains to be determined.

Several studies have suggested that the prevalence of left ventricular hypertrophy in hypertensive adults ranges from 33 % to 81 % [26, 27]. LVH has been noted to be a risk factor for cardiovascular disease, cardiovascular morbidity, ventricular arrhythmias, and cardiovascular death [28, 29]. Abnormalities in left ventricular structure are also present in up to 40 % of children and adolescents with prehypertension and hypertension [30–35]. Although controversial, some evidence suggests that these cardiac alterations occur even in pediatric patients with "white coat hypertension" [34]. A recent study by Urbina et al. [36] measured several cardiovascular parameters, including left ventricular mass and carotid intimal–medial thickness (cIMT) in normotensive, prehypertensive, and hypertensive adolescents. The authors noted a gradual increase in LVM index in normotensive patients compared to both prehypertensive and hypertensive subjects [36]. 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 [36]. Richey et al. [37] detected associations between development of LVH and systolic blood pressure as well as 24-h systolic blood pressure load. 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 [38]. Patients with eccentric LVH demonstrated higher diastolic blood pressures [38].

However, the association between blood pressure elevations and LVH is not always consistent. 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 [33]. In this study, children with LVH were more likely to have a higher BMI and to be nonwhite compared to

those without LVH. After controlling for age, sex, and height, no associations between either causal or ambulatory blood pressure parameters at the initial visit and LVH were detected [33]. In agreement with these findings, a follow-up study demonstrated that African-American children with primary hypertension demonstrated a higher prevalence of obesity and LVH compared to non-African-American children, suggesting that race and ethnicity in addition to BMI may also influence cardiovascular risk in children with primary hypertension [39]. Hanevold noted similar associations between LVH and BMI above the 95th percentile, but in their study, Hispanic children demonstrated a higher prevalence of LVH [35].

Sladowska-Kozlowska et al. [40] recently analyzed LV geometry in 86 children following 1 year of antihypertensive therapy [40]. In this study, eccentric hypertrophy was the most common pattern of remodeling in patients with altered LV geometry [40]. Measures of oxidative stress, waist circumference, and dyslipidemia were significantly associated with development of altered LV geometry in contrast to blood pressure measurements [40]. However, normalization of LV geometry was noted using both non-pharmacologic and pharmacologic methods to control blood pressure [40]. Interestingly, patients with concentric hypertrophy were more resistant to therapy, and the authors postulated that the presence of concentric hypertrophy reflected long-standing or advanced hypertension [40]. Similar results have been noted in other studies suggesting that this patient population may require more intensive therapy [41].

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 [42]. Similar findings have been reported in pediatric patients with hypertension [43, 44]. Recently, Border et al. [45] compared the ventricular function of 50 pediatric patients with primary hypertension to 53 normotensive, healthy controls. 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 [45]. 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 [45]. When compared to the controls, 36 % of the hypertensive patients demonstrated abnormal left ventricular compliance primarily affecting those with concentric LVH [45]. 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 [45].

Vascular Structure

In parallel with cardiac abnormalities, hypertension induces alterations in the structure and function of the arterial tree [46]. The mechanisms underlying these changes are multifactorial and incompletely understood [46, 47]. 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 [47]. Because elastin influences smooth muscle proliferation and migration, this redistribution of elastin fibers leads to dedifferentiation of smooth muscle cells and arterial wall hypertrophy [48]. Mechanical stress also alters the activity of matrix metalloproteinases which are essential for maintenance of the extracellular matrix of the arterial wall [47]. Continued wall stress enhances production of endothelin, a potent vasoconstrictor which when combined with other inflammatory mediators contributes to significant endothelial dysfunction. The physiologist Bjorn Folkow hypothesized that repeated adrenergic spikes in blood pressure coupled with structural modifications as well as an increased vessel wall/lumen ratio contribute to the establishment of high peripheral resistance and maintenance of elevated blood pressures [49]. Ultimately, these changes lead to structural reduction of the arterial lumen diameter and increased arterial stiffness [47].

To evaluate these alterations, vascular ultrasound has emerged as a noninvasive means to

assess changes in vascular structure and risk of future cardiovascular events [50]. 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 [50]. In a study of 32 patients referred to a pediatric hypertension clinic, 28 % of the patients demonstrated increased cIMT [51]. 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 [51]. Similarly, in the Bogalusa Heart Study, office-based systolic and diastolic blood pressures in childhood did not predict cIMT in adulthood [52]. Lande et al. [53] 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. These results demonstrated that cIMT was increased in hypertensive children relative to controls independent of BMI [53]. 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 [53]. 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 [54]. cIMT was associated with systolic blood pressure, pulse pressure, and BMI [54]. 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.

In addition to cIMT, pulse wave velocity is a widely used noninvasive method to assess arterial stiffness [55]. 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 [55]. However, in the presence of noncompliant 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 [56]. A recent report demonstrated that pulse wave velocity is increased in hypertensive adolescents compared to normotensive controls [57]. In a separate report, elevated mean blood pressure independently predicted elevated pulse wave velocity in a larger cross-sectional study of over 200 adolescents [58]. Together, these studies suggest that arterial compliance and elasticity are impaired early in hypertension.

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 3,000 accident victims aged 15–34 years who underwent autopsy [59]. In their analysis, hypertension significantly augmented the risk for development of atherosclerosis in the cerebral arteries [59]. In a separate follow-up study, hypertension also enhanced formation of raised lesions from fatty streaks in the abdominal aortas [60]. Interestingly, this association was only observed in African-American subjects and not in white subjects [59, 60]. 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 [61]. 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 [62, 63]. Together, these studies suggest that elevated blood pressure contributes to both initiation and progression of atherosclerosis.

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 [64]. In adults, abnormal FMD or endothelial dysfunction is associated with development of increasing cIMT and left ventricular mass even in patients with prehypertension [65]. Similar alterations in FMD were seen in pediatric patients with obesity, diabetes, as well as hypertension [66]. Lazdam et al. studied a group of normotensive adolescents over 10 years who were noted to have persistent endothelial dysfunction [67]. 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 [67]. 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 [68]. As a result, these arterial modifications may be precursors of hypertension as opposed to secondary complications [68].

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 [69]. 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 [70]. Loss of renal autoregulation as a result of arterial stiffening, low-grade chronic inflammation, oxidative stress, and altered renin-angiotensin-aldosterone activity are all thought to contribute to renal dysfunction in the context of hypertension [70]. 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. For example, the presence of microalbuminuria is thought to be an early marker for hypertensive renal disease [71]. More importantly, microalbuminuria is associated with increased risk of cardiovascular as well as all-cause mortality in adult patients with primary hypertension [72]. As part of the Bogalusa Heart Study, Hoq et al. [73] demonstrated that elevated childhood blood pressure was associated with the development of microalbuminuria in young African-Americans. 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 [73]. In agreement with these findings, Lubrano et al. [74] 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^2). Moreover, proteinuria was increased in patients with prehypertension (145 vs. 66 mg/m^2/24 h) [74]. 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 [74].

In a separate study, children with primary hypertension confirmed by ABPM have been shown to have higher urinary albumin excretion compared to controls [75]. Studies have also linked the development of changes in renal function to development of cardiovascular complications in hypertensive pediatric patients. Specifically, Assadi [76] examined the relationship between left ventricular hypertrophy, microalbuminuria, and C-reactive protein (CRP). In this study, estimated GFR, blood pressure, and left ventricular mass (LVM) were determined in 64 patients referred to a pediatric nephrology clinic.

The results demonstrated a correlation between blood pressure, LVH, and presence of microalbuminuria [76]. In regression analysis, CRP, microalbuminuria, and systolic blood pressure were independent predictors of LVH [76]. The author speculated that inflammation and microalbuminuria portend increased cardiovascular risk in pediatric patients with hypertension [76]. As a result, pharmacologic regimens that target these parameters may improve cardiovascular outcomes in this patient population [76].

The Retina

In a recent study of 800 hypertensive adult patients, the prevalence of early retinal vascular changes was 78 % using direct ophthalmoscopy [77]. 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 [78]. Several population-based studies have also suggested that individuals with retinal microvascular changes have increased cardiovascular morbidity and mortality [79]. 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 [80]. 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 % [81]. In a separate study, Daniels et al. [82] 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 [82]. 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 [83]. Mitchell et al. examined retinal arteriolar caliber in two cohorts of patients ages 6–8 and determined that each 10 mmHg increase in systolic blood pressure was associated with arteriolar narrowing by 2.08 μm independent of body size, birth parameters, and age [84].

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 [85]. Although the etiology of these lesions is unclear, several studies have suggested that elevated blood pressure impairs cognitive functioning in adults [85]. Recently, the Maine–Syracuse Study examined the cognitive functioning of approximately 1,500 patients using multiple domains on the Wechsler Adults Intelligence Scale [86]. Significant inverse associations between blood pressure parameters and cognitive functioning were observed including measures of psychomotor speed, concept formation, and abstract reasoning abilities [86]. Although limited by its cross-sectional design, these results indicated that hypertension is associated with poor performance in several aspects of cognition [86].

As discussed in more detail in Chap. 30, 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 [87]. 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 [88]. Adams et al. [89] 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 % [89]. The physiologic basis of these neurocognitive deficits is poorly understood. However, hypertension has been associated with changes in cerebral vascular reactivity [90]. In a study of 56 pediatric patients, cerebrovascular reactivity was measured in response to hypercapnia and was decreased relative to controls suggesting increased vascular resistance and

increased compliance [90]. Although not described in children, adults with hypertension have been noted to have alterations in the frontal lobe on imaging studies [91].

Sequelae of Acute Hypertensive Crisis

Central Nervous System

Central nervous system abnormalities are typically the most prevalent end-organ complications in hypertensive crises in children [92, 93]. Cerebral autoregulation is responsible for maintaining constant cerebral blood flow despite alterations in blood pressure [94]. However, as mean arterial pressure increases, disruption of the vascular endothelium and blood–brain barrier leads to fibrinoid deposition within the vascular lumen [95]. 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 [95]. As an imbalance between oxygen supply and demand develops, cerebral infarction can develop [95]. 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 % [96]. 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 [97–100]. Browning et al. [99] 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 [99]. In contrast, Logan et al. [100] reported three cases with permanent reductions in visual acuity despite normal-appearing optic discs. In terms of neurocognitive outcomes, Trompeter et al. [101] found that outcomes were not significantly different when compared to a control group that consisted of children with chronic renal disease.

Cardiovascular System

Cardiovascular complications are also common in severe hypertension [93]. 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 [102]. In an attempt to compensate for increased LV tension, myocytes become hypertrophic [103]. In addition, enhanced deposition of extracellular matrix within the ventricle occurs, further increasing the oxygen demand of the heart. Continued activation of the RAAS axis results in enhanced sodium absorption and increased total body water, further worsening ventricular load [102]. Because of increased metabolic demands, focal ischemia can develop, impairing both left ventricular contraction and relaxation [103]. Ultimately, the left ventricle is unable to overcome the abrupt increase in systemic vascular resistance causing left ventricular failure and congestive heart failure [104]. 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 [96]. It is important to emphasize that clinical findings of congestive heart failure are especially common in neonates with severe hypertension [105].

The Kidneys

Acute renal insufficiency due to altered renal autoregulation and subsequent renal ischemia is also a known complication of severe hypertension [103]. 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. Histologic 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 [106]. The presence of thrombosis and microangiopathic hemolysis is thought to portend a poor prognosis [107]. In a study of 51 adult patients with malignant hypertension, 46 patients demonstrated renal insufficiency with 67 % of the patients presenting with a serum creatinine greater than 2.3 mg/dl [108]. More importantly, 30 % of the patients in the study remained on chronic hemodialysis [108]. In a study by Gudbrandsson, 50 % of patients in hypertensive crisis presented with renal failure [109]. 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 [110–112]. Development of significant hematuria and proteinuria was also detected in these patients [110, 112].

Conclusions

The evidence discussed above demonstrates that subclinical alterations in end-organ structure and function occur early in the course of pediatric hypertension. Although the significance of these findings in the pediatric population requires additional longitudinal investigation, similar end-organ changes in the adult population portend poor cardiovascular morbidity and mortality. Since treatment of blood pressure in the adult population has been shown to improve outcomes, prompt recognition and treatment of hypertension in the pediatric population are imperative. But more importantly, these studies highlight the importance of defining appropriate blood pressure targets in the pediatric population to improve the long-term outcomes of these patients.

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Cognitive and Behavioral Aspects of Childhood Hypertension

30

Marc B. Lande, Juan C. Kupferman, and Heather R. Adams

Abstract

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 CW. Ambulatory blood pressure monitoring and hypertensive target-organ damage in children. Blood Press Monit. 1999;4 3–4:161–4; Lande MB, Carson NL, Roy J, Meagher CC. Effects of childhood primary hypertension on carotid intima media thickness: a matched controlled study. Hypertension 2006;48 1:40–4). 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 (Sharma M, Kupferman JC, Brosgol Y, Paterno K, Goodman S, Prohovnik I, et al. The effects of

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hypertension on the paediatric brain: a justifiable concern. Lancet neurol 2010; 9 9:933–40; Wong LJ, Kupferman JC, Prohovnik I, Kirkham FJ, Goodman S, Paterno K, et al. Hypertension impairs vascular reactivity in the pediatric brain. Stroke 2011; 42 7:1834–8). This chapter reviews emerging preliminary evidence that children with hypertension may also manifest more subtle adverse effects on the brain.

Keywords

Hypertension • Neurocognition • Cerebrovascular reactivity • Brain • Target-organ damage • Chronic kidney disease

Studies of Cognition in Hypertensive Adults: Implications for Children

Studies in adults show that hypertension is associated with negative effects on cognition, which range from mildly decreased performance on neurocognitive testing within the normal range of cognitive functioning to overt dementia [5]. 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 [6–8]. Furthermore, there is evidence of a genetic predisposition to performance deficits on neurocognitive testing among hypertensive adults with a parental history of hypertension [9]. 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 [5]. 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 [10].

Review of the literature on adults with hypertension underscores two 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 [11], 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 [6]. 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 [12, 13].

Studies in Children with Primary Hypertension

There is emerging, preliminary evidence that children with primary hypertension manifest neurocognitive differences when compared to normotensive controls [14]. 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

Table 30.1 Comparison of neurocognitive test scores of participants in NHANES III with SBP≥90th % to those with normal SBP

Cognitive test	SBP<90th %	SBP≥90th %	P-value
Block design	9.5±0.10	8.6±0.35	0.03
Digit span	8.7±0.08	7.9±0.24	0.01
Math	93.8±0.54	89.6±1.4	0.01
Reading	92.1±0.53	89.5±2.3	NS

Mean±SE
Adapted with permission from J Pediatr 2003 Dec; 143(6):720–724 [14]
NS not significant

representative sample of noninstitutionalized US children and adults [15]. 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 [13]. Children with systolic BP (SBP) ≥90th percentile had lower average scores compared with normotensive children for Digital Span, Block Design, and mathematics (Table 30.1). 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 ≥95th 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 [16]. 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 [17, 18]. 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 [19]. 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 observations in adults, both hypertensive and control children obtained scores within the clinically normal range in comparison to same-age peers, and there was no difference in the small proportion of hypertensive and normotensive subjects scoring in the clinically significant range (Table 30.2).

In the same study [16], parents also completed the Achenbach Child Behavior Checklist (CBCL), another parent rating scale that measures a range of childhood emotional and behavioral problems [20]. 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

Table 30.2 Comparison of baseline parent rating scale results of normotensive and hypertensive subjects

	Normotensives	Hypertensives	
Rating scale[a]	N = 31	N = 32	P-value
BRIEF (T-scores)			
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
CBCL (T-scores)			
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

Adapted with permission from J Pediatr 2009;154(2):207–212 [15]
[a]Median (interquartile range)

internalizing behaviors, and more than one-third of hypertensive subjects had internalizing behaviors in the clinically significant range (Table 30.2). 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 [21]. 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 significance of such mild differences is unclear. However, a recent study showed that children with hypertension do manifest learning and attention problems [22]. 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 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 [23]. The authors acknowledged that some of the subjects with ADHD may have had increased BP because they were receiving stimulants for inattention [24], 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.

Studies in Children with Chronic Kidney Disease

Children with chronic kidney disease (CKD) are at risk for cognitive dysfunction, and over half have hypertension [25]. 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 [26]. 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 [27]. The relation between cognition and hypertension was recently evaluated in the Chronic Kidney Disease in Children (CKiD) study population, a cohort of children with mild-to-moderate CKD [28]. CKiD subjects had both auscultatory BP 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.

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 [29, 30]. 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 [31].

Data on the effects of antihypertensive therapy on neurocognitive measures in children are very 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) [32]. The subjects in this report were the participants from the prior study

Table 30.3 Comparisons of parent rating scale T-scores, adjusted for age and socioeconomic status, from baseline to the 12-month assessment

	Control			Hypertensive		
	N = 25			N = 22		
Parental assessment	Baseline	Follow-up	P-value	Baseline	Follow-up	P-value
BRIEF						
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
CBCL						
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

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of baseline parental assessments described above [16] 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 from baseline to 12 months. Scores on the parent BRIEF improved in hypertensive subjects but not controls, with scores being statistically indistinguishable between groups at 12 months (Table 30.3). Furthermore, subjects felt to be most at risk for target-organ damage (baseline left ventricular hypertrophy and/or systolic BP load ≥ 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 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 [33]. However, an alternative preliminary hypothesis suggested the possibility that the brain may be affected even before the blood vessels [34]. According to this "brain as essential" hypothesis, the brain participates in the development of high BP and can also be affected by it. Hence, it is possible that essential hypertension may induce changes on the brain prior or concomitantly to the effects on the vasculature.

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 [35, 36]. 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.

Table 30.4 Cerebrovascular reactivity prospective studies in young hypertensive subjects

Publication	Population	Main results
Settakis et al. [33]	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 ± 23.7 versus 114.8 ± 27.6, $p = 0.07$ (HT vs. control) DBP 52.0 ± 16.4 versus 53.1 ± 16, $p = 0.67$ (HT vs. control)
Settakis et al. [34]	58 normotensive and 113 HT adolescents	Change in flow velocities was decreased in HT versus controls Systolic blood flow 21.0 ± 19.0 versus 25.9 ± 12.5, $p < 0.05$ Diastolic blood flow 40.4 ± 18.1 versus 45.5 ± 15.2, $p < 0.05$
Páll et al. [35]	59 normotensive, 47 WCH, and 73 HT adolescents	Mean blood flow velocity change was lower in WCH = 5.3 ± 3.1 % and HT = 9.5 ± 2.6 % compared to normotensive controls = 12.1 ± 2.2 %
Wong et al. [4]	9 normotensives, 9 pre-HT, 18 WCH, and 13 untreated HT and 7 treated HT children and adolescents	TCD reactivity was lower in untreated HT = 2.556 ± 1.832 cm/s/mmHg compared to normotensive controls = 4.256 ± 1.334 cm/s/mmHg ($p < 0.05$)

Adapted with permission from Pediatr Nephrol 2012 Jun, epub ahead of print [43]
HT hypertensive, *WCH* white-coat hypertension

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 30.4). 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 30s of breath-holding (breath-holding test), as a vasodilatory stimulus [37], and at rest and after 60s of voluntary hyperventilation, as a vasoconstrictory stimulus [38]. 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 vasoconstrictory ability of the cerebral arterioles, consistent with decreased cerebrovascular reactivity among hypertensives compared to healthy controls.

In a more recent 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 [39]. Reactivity to carbon dioxide (CO_2) was diminished in both white-coat hypertensive and hypertensive subjects, compared to controls, also suggesting abnormal cerebrovascular reactivity.

In another recent 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_2. Cerebrovascular reactivity during hypercapnia was quantified by time-averaged maximum mean cerebral blood flow velocity and end-tidal CO_2. This study also found that children and adolescents with untreated hypertension had significantly lower hypercapnic reactivity compared to normotensive controls [4]. In this study, the baseline mean DBP was inversely related to reactivity, suggesting that DBP may be a better predictor of cerebral end-organ damage than SBP.

In summary, preliminary studies have showed 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.

Furthermore, researchers have suggested that the neurocognitive deficits described in children and adolescents with hypertension may be secondary to abnormal cerebrovascular reactivity [4]. Although there are no published studies addressing the effects of elevated BP on both cerebrovascular reactivity and cognition in children, alterations in cerebral blood flow and possible neurocognitive deficits have been described in other diseases (e.g., sickle cell disease[40], mild-disordered breathing[41]). Ongoing research will help clarify the relationship among elevated BP, abnormal cerebrovascular reactivity, and neurocognitive deficits in children and adolescents.

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 [42]. 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 [13], depression [43], and anxiety [13]. 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 [13]. Fourth, 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 [44]. 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.

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 [45].

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 and better delineate the long-term behavioral and cognitive impacts of childhood-onset hypertension.

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Hypertension and Cardiovascular Disease in Developing Countries

31

Vera H. Koch

Abstract

Hypertension is a major global chronic noncommunicable disease (NCD). One-quarter of the world's adult population has hypertension, and this is likely to increase to 29 % by 2025. 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 manifest CVD events. Compounding this high burden of hypertension is a lack of awareness and insufficient treatment in those with hypertension.

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. The combination of population-wide and individual interventions may save millions of lives and considerably reduce human suffering from NCDs.

Keywords

Hypertension • Developing world • Noncommunicable diseases • Global disease burden • Epidemiological transition • Early or fetal origins of adult disease • Malnutrition • Low birth weight

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Epidemiologic Transition and Health Statistics in Developing Countries

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 [1]. In developed countries, the health problems have largely been those associated with increased wealth, which enables expenditure of resources on poor health habits, such as a 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.

The present picture of health problems around the world, however, has changed. Noncommunicable diseases (NCDs) are the leading global causes of death, causing more deaths than all other causes combined, and they strike hardest at the world's low- and middle-income populations. Nearly 80 % of NCD deaths occur in low- and middle-income countries, and NCDs are the most frequent causes of death in most countries, except in Africa. Even in African nations, NCDs are rising rapidly and are projected to exceed communicable, maternal, perinatal, and nutritional diseases as the most common causes of death by 2030 [2]. Over 80 % of cardiovascular and diabetes deaths occur in low- and middle-income countries. NCDs also kill at a younger age in low- and middle-income countries, where 29 % of NCD deaths occur among people under the age of 60, compared to 13 % in high-income countries [2].

Hypertension is a major global chronic NCD. One-quarter of the world's adult population has hypertension, and this is likely to increase to 29 % by 2025. The absolute prevalence of hypertension in economically developed nations is ~37.3 % compared with 22.9 % in developing nations [3]. Hypertension is projected to be one of the major risk factors underlying the global burden of disease in 2020 [4]. However, as there is a much larger population in the developing world, the absolute numbers of patients affected by hypertension are considerably higher and are likely to grow as increased globalization and economic improvement lead to urbanization and longer life expectancy.

Changes that have traditionally occurred with economic development include change from times of high mortality and low population growth to periods of increased lifespan and periods of receding pandemics. The final progression is then on to degenerative and man-made diseases, such as cardiovascular disease (CVD), resulting from major social and economic changes [1]. 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 [5]. Life expectancy in developing countries has risen, due to a decline in deaths occurring in infancy, childhood, and adolescence, to increased effectiveness of public health responses to perinatal, infectious, and nutritional deficiency disorders and to improved economic indicators 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 manifest CVD events [6, 7] and leading to a projected rise in both proportional and absolute CVD mortality rates in the developing countries [1].

The Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group estimated trends and their uncertainties in mean systolic blood pressure (SBP) for adults 25 years and older in 199 countries and territories. Data was obtained from published and unpublished health examination surveys and epidemiological studies (786 country-years and 5.4 million participants). For each sex, a Bayesian hierarchical model was used to estimate mean SBP by age, country, and year, accounting for whether a study was nationally representative. In 2008, age-standardized mean SBP worldwide was 128.1 mmHg in men and 124.4 mmHg in women. Globally, between 1980 and 2008, SBP decreased by 0.8 mmHg per decade in men and 1.0 mmHg per decade in women. Female SBP decreased by 3.5 mmHg or

more per decade in Western Europe and Australasia. Male SBP fell most in high-income North America, by 2.8 mmHg per decade, followed by Australasia and Western Europe, where it decreased by more than 2.0 mmHg per decade. SBP rose in Oceania, East Africa, and South and Southeast Asia for both sexes and in West Africa for women, with the increases ranging 0.8–1.6 mmHg per decade in men (posterior probabilities 0.72–0.91) and 1.0–2.7 mmHg per decade for women (posterior probabilities 0.75–0.98). Female SBP was highest in some East and West African countries, with means of 135 mmHg or greater. Male SBP was highest in Baltic and in East and West African countries, where mean SBP reached 138 mmHg or more. Men and women in Western Europe had the highest SBP in high-income regions. These data confirm that SBP is currently highest in low-income and middle-income countries [8].

The Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group reports that, in adult men and women, obesity is increasing in all regions of the world. In 2008, 1.46 billion adults were overweight (BMI≥25 kg/m^2), including 500 million who were obese (BMI≥30 kg/m^2) [9]. BMI was substantially higher in high-income countries (mean BMI 24·7 kg/m^2 in 1980 and 26.6 kg/m^2 in 2008) and in middle-income countries (23.6 and 26.1 kg/m^2) compared to low-income countries (20.7 and 22.3 kg/m^2), but increased in all regions, so that BMI is now similar in high-income and middle-income countries. This result suggests that overweight affects one in three adults and obesity affects one in nine adults in the world – a tsunami of obesity that will eventually affect all regions of the world [10].

Fasting total cholesterol concentrations were highest in high-income countries in 1980 and 2008 (5.62 and 5.19 mmol/L), followed by middle-income countries (4.91 and 4.70) and low-income countries (4.46 and 4.20). The greatest decreases occurred in Western high-income countries and in eastern and central Europe (0.2 mmol/L per decade). By contrast, increases in cholesterol occurred in east and Southeast Asia and Pacific subregions (0.08–0.09 mmol/L per decade). Notably Japan, China, and Thailand all showed increases in total cholesterol [11]. Understanding the reasons for the contrasting global changes in blood pressure, obesity, and total cholesterol will provide useful insights that could help to mitigate the adverse effects of the epidemic of obesity more rapidly than the necessary societal and structural changes needed to reverse the prevalence of obesity itself [10].

The risk factors underlying the emergence of NCDs include increased levels of alcohol consumption, tobacco smoking, obesity, physical inactivity, and low fruit and vegetable intake [2, 12]. Several studies from different continents have documented the higher prevalence of hypertension in urban versus rural populations [3, 13–17]. 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 [5, 18].

An aggravating factor in the CVD epidemic in developing countries might be that the normal range of BMI cutoff values derived in the Western population may be misleading when used for other ethnic groups [19]. 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 [19, 20].

Genetic differences may also 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 with a greater than expected increase in ambulatory systolic BP to any given body mass index in African-descent hypertensive patients [21], a of lack of stimulation of plasma renin activity by natriuresis with furosemide suggesting a hyporesponsive RAAS in hypertensive urban Zulus [22], and the high prevalence of salt-sensitive hypertension in hypertensives of African descent pointing to an abnormal renal hemodynamic adaptation during high salt intake [23].

The emergence of the CVD epidemic in developing countries during the past two to three

decades has attracted little public health response, even within these countries. In a recent literature search of the MEDLINE database for published studies reporting the prevalence of hypertension in representative population samples [24], the reported prevalence of hypertension varied around the world, with the lowest prevalence in rural India (3.4 % in men and 6.8 % in women) and the highest prevalence in Poland (68.9 % in men and 72.5 % in women). Awareness of hypertension was reported for 46 % of the studies and varied from 25.2 % in Korea to 75 % in Barbados; treatment varied from 10.7 % in Mexico to 66 % in Barbados and control (blood pressure < 140/90 mmHg while on antihypertensive medication) varied from 5.4 % in Korea to 58 % in Barbados. It can be concluded that although hypertension is an important public health challenge in both economically developing and developed countries, significant numbers of individuals with hypertension are unaware of their condition and, among those with diagnosed hypertension, treatment is frequently inadequate [7, 24].

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 [25–34]. 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 [35–37].

In 1992, Hales and Barker [38] coined the term the "thrifty phenotype" hypothesis, derived from the prior "thrifty genotype" hypothesis [39] proposed by Neel to suggest that "thrifty" genes were selected during evolution at a time when food resources were scarce and that they resulted in a "fast insulin trigger" and thus an enhanced capacity to store fat, which placed 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 [38, 40].

This concept is consistent with the definition of "programming" as proposed by Lucas in 1991 [41] 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 [42, 43]. 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 [44–46]. As in other species, developmental plasticity attempts to "tune" gene expression to produce a phenotype best suited to the predicted later environment [47] when the resulting phenotype is matched to its environment, the organism will remain healthy. When there is a mismatch, 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 [48].

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 [49] 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 [50] 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. 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 [51].

The degree of mismatch can by definition be increased by either poorer environmental conditions during development or richer conditions later, or both [48]. Such changes are of considerable importance in developing societies going through rapid socioeconomic transitions and represent an important risk factor for CVD in the populations of developing countries as vast numbers of poorly nourished infants have been born in the past several decades and have been benefitting from a steady improvement in child survival, which will lead to a higher proportion of such infants surviving to adult life.

Evidence of Epigenetic Mechanisms in Animals and Its Importance as a Cause of Adult Nephropathy and Arterial Hypertension

Birth weight is a crude 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 [52]. 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, including nephrons [53].

In the years since, investigators have induced such developmental programming of adverse health outcomes in many animal species with the use 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 [44]. 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 [44].

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 [54]. In the late 1980s, Brenner et al. advanced the argument that deficiency in glomerular filtration surface area may be a major cause of essential hypertension [55]. Several animal studies were devised to evaluate the effect of perinatal interventions on renal organogenesis and postnatal renal function. Table 31.1 depicts some of these studies and the main results in the offspring [56–61].

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.

Table 31.1 A selection of intervention studies performed in pregnant rats to evaluate renal organogenesis and postnatal renal function in the offspring

Author	Intervention	Outcome
Gilbert et al. [56]	Late gestational exposition to gentamicin	Oligonephronia Early nephron compensatory adaptation Progressive glomerular sclerosis
Celsi et al. [57]	Gestational exposition to dexamethasone	Oligonephronia Early nephron compensatory adaptation Arterial hypertension ⇓ GFR Albuminuria ⇓ Urinary sodium excretion rate and fractional sodium excretion ⇑Sodium tissue content was higher
Lelièvre-Pégorier et al. [58]	Gestational exposition to mild vitamin A deficiency	Oligonephronia
Vehaskari et al. [59]	Gestational exposition to low-protein diets	Oligonephronia Apoptosis ⇓PRA ⇑Aldosterone Arterial hypertension
Woods et al. [60]	Gestational exposition to low-protein diets	Oligonephronia Glomerular enlargement ⇓ Renal renin mRNA Arterial hypertension
Pham et al. [61]	Uteroplacental insufficiency	Oligonephronia Apoptosis Arterial hypertension

Patterns of smoking, diet, and exercise can affect risk across more than one generation [62]. 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 [63]. 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 [64]. 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 [63].

Support for the Brenner hypothesis came from observations by Keller et al., who found fewer nephrons at postmortem in individuals with essential hypertension [65]. 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 [66].

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 [67]. There is also evidence of reduced nephron endowment in severely disadvantaged populations, such as Aboriginal people living in remote parts of Australia, in which there is an ongoing epidemic of hypertension and chronic kidney disease [68]. 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 [68].

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;

Table 31.2 List of selected epidemiological studies investigating the association of birth weight and/or prematurity with different clinical outcomes along the human life cycle in developing countries and underprivileged populations

Author	Country	Population	Outcome	Aggravating influence
Levitt et al. [84]	South Africa	5-year-old children	Inverse relation between BW and SBP	–
Law et al. [85]	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. [86]	Jamaica	11–12-year-old children	Inverse relation between SBP and BW	Postnatal growth retardation Current WT
Barros and Victora [87]	Brazil	14–15-year-olds	No association between BW and BP	Arterial hypertension more frequently diagnosed in adolescents born SGA
Nelson et al. [88]	PIMA Indians (USA)	Adults Type 2 diabetes	Association of ↑ albuminuria with BW < 2.5 kg BW > 4.5 kg	
Hoy et al. [89]	Australian Aborigines	Adults	Inverse relation between BW and albuminuria	
Bavdekar et al. [90]	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 [91]	Filipines	14–16-year-olds	Higher prevalence of elevated BP in low-BW males	Weight gain from late childhood into adolescence in males with low BW

Stunting: height for age < −2 SD of the NCHS references
BP blood pressure, *SBP* systolic blood pressure, *BW* birth weight

the most probable candidates are high salt intake, age, and altered renin-angiotensin-aldosterone system function. As a consequence, 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 [69]. Further discussion of the effects of perinatal programming on blood pressure can be found in Chap. 7.

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 [29, 33, 34, 70]. These observations have been corroborated and extended by other epidemiologic studies and studies in twins [71–81].

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? [82]. The low-birth-weight group includes those born small for gestational age (SGA), premature, or following in vitro fertilization (IVF), 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 >2,500 g [83].

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 31.2 [84–91].

The Future of Cardiovascular Disease in Developing Countries

As a consequence of the epidemiological transition, life expectancy in developing countries has risen; the increasing longevity provides longer periods of exposure to the risk factors for CVD, resulting in a greater probability of clinically manifest CVD events [7]. 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 World Health Organization [92], 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 [2, 93]. Table 31.3 shows the WHO data on percentage and number of low-birth-weight infants (LBW) according to the world region and WHO development classification in 2000 [94]. The high prevalence of short stature in children of developing countries, a well-known sign of chronic malnutrition, is depicted in Fig. 31.1, showing high rates in important areas of the developing world, including India [95].

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" [96] and the "Making pregnancy safer" program [97] 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

Table 31.3 Percentage and number of low-birth-weight infants (LBW) according to the world region and WHO development classification, 2000 (Modified from [94])

	Percentage of LBW	Number of LBW/1,000	Number of live births/1,000
World	15.5	20,629	132,882
Developed	7.0	916	13,100
Less developed	16.5	19,713	119,721
Africa	14.3	4,320	30,305
Asia	18.3	14,195	77,490
Europe	6.4	460	7,185
Latin America and Caribbean	10.0	1,171	11,671
North America	7.7	348	4,479
Oceania	10,5	27	255

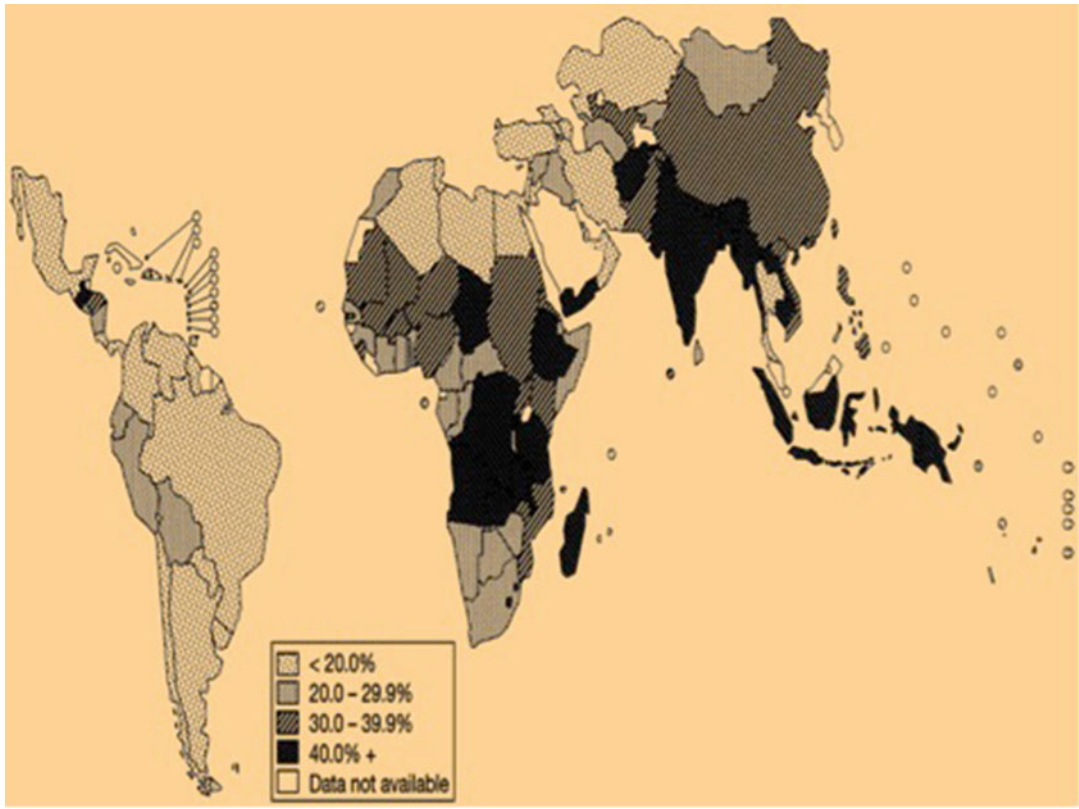

Fig. 31.1 Prevalence of short stature in children younger than 5 years of age in developing countries [95]

early childhood, which are associated with the use of nutrient-enriched formula and may predispose to hypertension and metabolic syndrome in later life [98, 99]. Schoolchildren and adolescents cannot be forgotten as it is mandatory to ensure their access to a properly balanced nutrition and lifestyle orientation, which includes alcohol and tobacco avoidance, daily exercise, and weight control [100].

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 [101].

Unfortunately, low- and middle-income countries face many competing priorities for investment and end up committing less financial resources to health. As an example, the United States spends more than $7,000 per capita on health, whereas Eritrea spends less than US $10 [102]. As a consequence in poorer countries, most health-care costs must be paid by patients out of pocket, and the cost of health care for NCDs creates significant strain on household budgets, particularly for lower-income families. 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. Country 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 [2].

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 World Health Organization (WHO) has taken a lead role in the development of global strategies for the prevention of NCDs such as hypertension and their risk factors. The WHO STEPwise approach to Surveillance (STEPS) program is low cost and aimed at promoting CVD risk factor surveillance in developing countries [103]. 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 [104].

Interventions to prevent NCDs on a population-wide basis are not only achievable but also 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 noncommunicable diseases 2010 (2), 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
- Raising taxes on alcohol
- Reduce salt intake and salt content of food
- Replacing trans fat in food with polyunsaturated fat
- Promoting public awareness about diet and physical activity, including through mass media

In addition to best buys, there are many other cost-effective and low-cost population-wide interventions that can reduce risk factors for NCDs. These include the following interventions:

- 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

Also, there is strong evidence, though currently a shortage of cost-effectiveness research, for the following interventions:

- 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. A combination of population-wide and individual interventions can reproduce successes in many more countries through cost-effective initiatives that strengthen overall health systems. 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 [105].

The NCD epidemic exacts an enormous toll in terms of human suffering and inflicts serious damage to human development in both the social and economic realms. The epidemic already extends far beyond the current capacity of lower-income countries to cope with it, which is why death and disability are rising disproportionately in these countries. This state of affairs cannot continue. There is a pressing need to intervene. Unless serious action is taken, the burden of NCDs will reach levels that are beyond the capacity of all stakeholders to manage [2].

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Part IV

Evaluation and Management of Pediatric Hypertension

Evaluation of Hypertension in Pediatric Patients

32

Joyce P. Samuel, Rita D. Swinford, and Ronald J. Portman

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. The first phase seeks to answer whether the patient is truly hypertensive in the nonmedical setting. This can be confirmed with either ambulatory blood pressure monitoring or self-monitored blood pressure monitoring. Once it is determined that the patient is truly hypertensive, the second phase provides screening for etiology of hypertension, hypertensive end-organ damage, and comorbidities. The third phase of evaluation defines the underlying abnormality which could be causing the hypertension, and the fourth phase determines the significance and remediability of the abnormality. By systematically using the four phases outlined in this chapter, the clinician can conduct a thorough evaluation of the hypertensive patient.

Keywords

Primary hypertension • Secondary hypertension • Ambulatory blood pressure monitor • Diagnosis • Evaluation

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Introduction

A clinical challenge to the successful treatment of children with hypertension is in the identification and then thorough evaluation of children with elevated blood pressure (BP) [1]. In this light, consideration can be given to the causative spectrum of hypertension in pediatric patients as it is broad and changes with age. The identification of a secondary cause of hypertension can give clues to the mechanism of the hypertension, which may

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Table 32.1 Classification of hypertension in children 1 year of age and older and adolescents

Normal blood pressure	SBP and DBP less than the 90th percentile
Prehypertension	SBP or DBP >/= to the 90th percentile but < the 95th percentile
Hypertension	SBP or DBP >/= to the 95th percentile
Stage 1 hypertension	SBP or DBP from 95th percentile to 99th percentile plus 5 mmHg
Stage 2 hypertension	SBP or DBP > the 99th percentile plus 5 mmHg

Percentiles are for sex, age, and height for blood pressure measured on at least three separate occasions
Characterize by higher percentile if SBP or DBP percentiles are different
Adapted from National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents [2]
SBP systolic blood pressure, *DBP* diastolic blood pressure

direct the choice of antihypertensive therapy. In some cases, discovering a clear secondary cause of hypertension can even identify a condition with a definitive cure, such as renal artery stenosis.

Most infants, toddlers, and school-aged children must be presumed to have secondary hypertension, with primary hypertension most prevalent in adolescence. For children with stage 2 hypertension (BP levels that are greater than 5 mmHg above the 99th percentile), careful, comprehensive, and immediate evaluation is required. A rule of thumb for the identification of children with secondary hypertension is that it is more likely to be found in the youngest and most severely hypertensive. However, this may not always be the case, and therefore, a thoughtful evaluation in all children is important as the cause may be remediable or may point to a preferred class of pharmacologic therapy. Recommendations for pharmacologic treatment are based on the presence of symptomatic hypertension, evidence of end-organ damage and/or stage 2 hypertension, or stage 1 hypertension unresponsive to lifestyle modification (Table 32.1) [2]. Not to be discounted are children in high-risk diagnostic groups, e.g., diabetes mellitus and chronic kidney disease (CKD), whose onset of premature atherosclerosis leads to early cardiovascular disease. Recent recommendations for treatment based on risk stratification by disease process are now available [3].

Unlike in adults, the diagnosis and treatment of pediatric hypertension predominantly is founded on extrapolations from secondary endpoints, such as target organ damage, rather than being driven by evidence-based outcomes of cardiovascular morbidity and mortality [2]. Recently, however, a 5-year randomized trial was published showing the benefit of strict BP control using renoprotective therapy on retarding the progression of renal disease in children [4]; hopefully, this will lead to further development of evidence-based treatment recommendations. The necessity for additional studies and revised guidelines has become increasingly clear as mounting evidence shows that even mild hypertension in children and adolescents is much more common than previously described [5, 6]. A shift in BP distribution to higher levels is now seen in children and adolescents, very likely secondary to the global obesity epidemic. We now understand that children with elevated BPs mature into adults with hypertension, and this underscores the importance of control [7].

Technologic advances have seen the widespread introduction of oscillometric devices for BP measurement which have the advantage of ease of use and little interobserver variability. These devices determine BP indirectly by determining the mean arterial pressure from the point of maximum oscillations and then by calculating the SBP and DBP using proprietary unpublished algorithms. Unfortunately, short oscillatory cycles, as is sometimes seen in children, can lead to errors in measurement. Validation of the oscillometric method is recommended, but few devices have been validated successfully [8]. Studies that compare oscillometric devices to auscultatory sphygmomanometry show poor correlation, highlighting the need for confirmation by auscultatory methods [9-11].

Since BP is a continuous variable, assuming a single clinic BP (CBP) measurement is representative of the patient's true BP pattern may not be acceptable. Ambulatory BP monitoring (ABPM), on the other hand, is considered to be superior to CBP for the prediction of cardiovascular events [12-15]. With this in mind, ABPM is now increasingly recognized as being indispensable for the diagnosis and management of hypertension [16-19]. Urbina et al., in a 2008 American Heart Association scientific statement, reported that the

24-h ABPM had utility in the assessment of hypertension in children and adolescents [18]. In children, not dissimilar to adults, ABPM is found to correlate with left ventricular mass in both hypertensive and normotensive patients. In children, however, a relationship is seen with LVM and nocturnal systolic BP and BP load [20, 21]. McNiece et al. in 2007 linked the severity of hypertension to the odds of having left ventricular hypertrophy [22]. Others have shown thicker carotid arteries with higher ABPM levels [23, 24]. ABPM may also facilitate the differentiation of primary from secondary hypertension as adolescents with secondary hypertension have been shown to have greater nocturnal systolic BP loads and daytime and nocturnal diastolic BP loads than similarly aged children with primary hypertension [25]. A more detailed discussion of ABPM can be found in Chap. 11.

There is limited evidence on the use of home BP measurement in children and adolescents, but it can be a technique for BP monitoring, suggest the diagnosis of white coat hypertension (WCH), and monitor effectiveness of antihypertensive therapy. Wühl et al. in 2004 compared ABPM with self-measurement of BP and clinic BPs in children with chronic kidney disease. They were able to show that while self-measured blood pressure (SMBP) did improve clinic BP's sensitivity to detect hypertension, 20 % of hypertensive children were missed, proving that ABPM remained superior in the evaluation of hypertension [26]. Home monitoring of BP in children and adolescents can be used as a supplement in the assessment of hypertension in clinical practice, particularly for the detection of white coat and masked hypertension. Home BP monitoring's advantages include lower cost and user acceptance [27]; however, as discussed in Chap. 9, one must carefully choose the device used for home monitoring of BP, as many marketed devices may not be validated for use in pediatric patients.

That said, 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. Indeed, with the exception of childhood asthma, hypertension may now be the most common chronic disease of childhood. The causal factor responsible for the apparent dramatic 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 [28]. Approximately 60 % of obese (BMI ≥ 95th percentile) adolescents have at least one risk factor for future cardiovascular disease, including elevation of BP, abnormal lipids, and insulin resistance [29].

Once it has been determined that a child has an elevated BP and that this BP elevation is persistent, the following guide is anticipated to aid in the diagnostic evaluation (Tables 32.2 and 32.3).

Table 32.2 Phases of hypertension evaluation

Phase 1: Is the patient truly hypertensive in the nonmedical setting?
Ambulatory blood pressure monitoring
Self-measured blood pressure
School-based blood pressure measurements
Phase 2a: Screening for etiology
Serum chemistries: electrolytes, creatinine, BUN
CBC
Urinalysis; Urine culture
Renal ultrasound with Doppler
Echocardiogram/EKG
Phase 2b: Identification of end-organ damage phase
Echocardiography
Retinal examination
Urine protein quantification
Phase 2c: Screening for comorbidities
Fasting insulin and glucose
Fasting lipoprotein profiling (serum total cholesterol, with high-density lipoprotein, low-density lipoprotein, and triglycerides)
Phase 3: Definition of abnormalities
Renal imaging
Renal ultrasound with Doppler
VCUG
Renovascular imaging (noninvasive), CT, or MRI angiography
Captopril challenge
Renin, aldosterone profiling
Thyroid function
Catecholamine profiling
Abdominal imaging; CT or ultrasound
Phase 4: Determination of significance and remediability of abnormalities
Arteriography (conventional or digital subtraction angiography)
Renal vein renin collection
Renal biopsy
MIBG scans

Table 32.3 Phase 2 evaluation: screening for etiology, end-organ damage, and comorbidities (to be done only *after* the hypertension is confirmed in Phase 1)

Test	Comments
Why does the patient have hypertension?	
Serum electrolytes	1^0 or 2^0 aldosteronism
BUN and serum Cr	Renal dysfunction
Hemoglobin/hematocrit	Renal dysfunction/anemia of CRF
Renal ultrasound	Anatomic etiology
Urinalysis	Hematuria/proteinuria (nephritis, renal masses)
What has hypertension done to the patient?	
Urinalysis	Renal injury (microalbuminuria, proteinuria)
Echocardiogram	Left ventricular hypertrophy
Fundoscopic exam	Arteriolar narrowing and AV nicking
What other risk factors for cardiovascular/kidney disease are present?	
Poor growth	Chronic kidney disease
Weight	Obesity
Fasting blood sugar, insulin	Diabetes
Elevated HgA1c	Diabetes
Glucosuria	Diabetes
Lipoprotein analysis	Hypercholesterolemia, hypertriglyceridemia
Family history	Cardiovascular, obesity
Personal history	Cardiovascular disease (medications, smoking, inactivity)

We use the term "phase" of evaluation in an attempt to lessen confusion with "stages" of hypertension used in Table 1.

Phase 1: Is the patient truly hypertensive in the nonmedical setting?
(Confirmation of hypertension with ABPM or objective SMBP)

Phase 2: Screening for hypertension

A. Why does the patient have hypertension? (etiology)
B. What has hypertension done to the patient's body already? (end-organ damage)
C. What other risk factor for cardiovascular/kidney disease does the patient have? (comorbidities)

Phase 3: Definition of abnormalities

Phase 4: Determination of significance and remediability of abnormality

Evaluation

Phase 1: Is the patient truly hypertensive in the nonmedical setting?

When a child is found to have an elevated BP, this should elicit, *before* a thorough evaluation is performed, confirmation of the possible hypertension. Preferably three measurements should be taken in an upper extremity at least 2 min apart and the average of these compared to the normative values from the Fourth Report at each measurement session [2]. Accurate measurement of BP is dependent on a number of factors including the use of the 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 [30]. If a BP cuff is used with an inappropriately small cuff, BP may be falsely overestimated.

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. SMBP can also be performed preferably with a recording monitor and with the caveats previously mentioned. School nurses can be useful in collecting additional measurements which can then be faxed to complete the record. School BP equipment is often not well calibrated, and the nurse's training may be

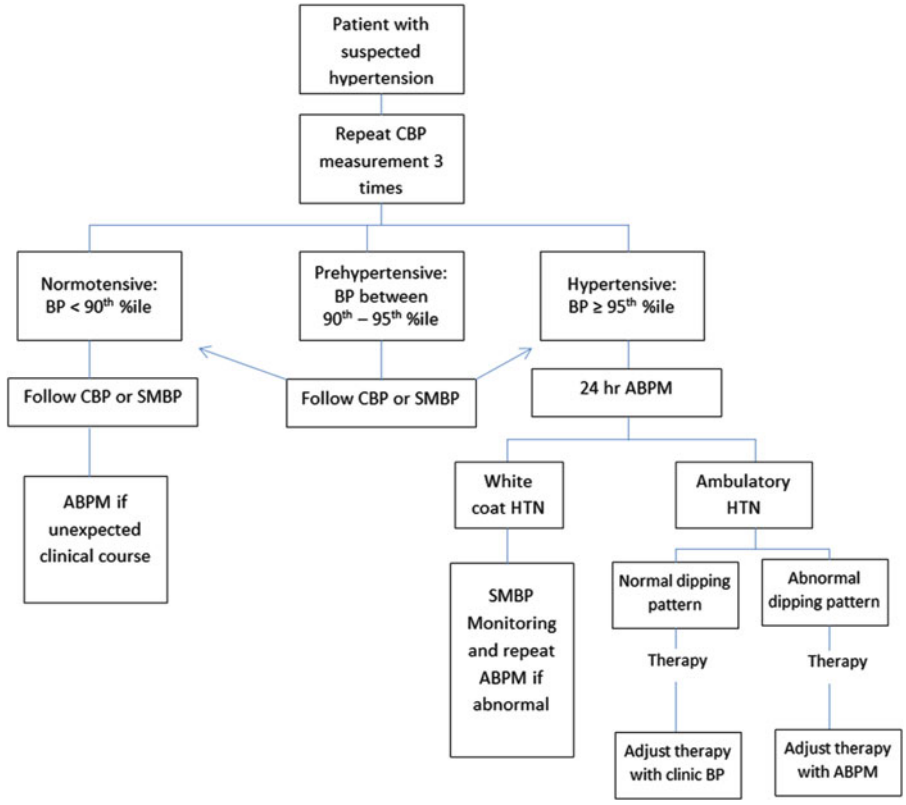

Fig. 32.1 When a patient is found to have an elevated BP on initial evaluation or screening, BP should be repeated at least twice. If the patient is determined to be normotensive after repeated measures, follow-up BP measurements should be taken every 6 months to a year. One must be mindful that the patient may still have a non-dipping pattern, placing them in a higher risk category or masked hypertension. One should follow the patient's clinical course and if proceeds as expected, CBP or SMBP can be used to follow the patient. However, if features are unexplained such as proteinuria or symptoms are present with elevation of BP, an ABPM should be performed. If the patient has hypertension by casual measurement, ABPM may be performed to diagnose WCH as well as determine altered BP patterns. If WCH is found, SMBP can be effective in monitoring the WCH, and ABPM can be repeated if clinical course varies from expected. If ABPM confirms the hypertension, the patient can then be categorized by a dipping status. A patient with a dipping pattern may be followed with CBP or SMBP with occasional ABPM monitoring as needed. However, a patient with a non-dipping pattern can only be practically monitored by ABPM which should be used along with CBP and SMBP as needed to maintain and assure adequate circadian BP control. The significance and chronicity of BP abnormalities should also be confirmed by assessment of end-organ damage

variable; therefore, proper training of the nurses and monitor validation at local schools is a time well spent. Ideally ABPM should be used to confirm the diagnosis of hypertension and to exclude the diagnosis of WCH [31]. One must also note that a small percentage of patients similar to those reported by Lurbe and colleagues [32] who have normal casual BP measurements have elevated ambulatory BP measurement, i.e., masked hypertension. An algorithm for the evaluation of hypertension using different BP measurement techniques can be found in Fig. 32.1. In the case where ABPM is unavailable, multiple CBP or self-measured BP can be used.

Phase 2: Screening for identifiable causes, comorbidities, and end-organ damage

a. *Why does the patient have hypertension?*

The most common etiologies of hypertension by age group are listed in Table 32.4. The exact percentages at each

Table 32. 4 Most Common Causes of Secondary Hypertension: By Age

Age Group	Etiology
Newborn	Renal artery or venous thrombosis Renal artery stenosis Congenital renal abnormalities Coarctation of the aorta Bronchopulmonary dysplasia History of Prematurity
First Year	Renovascular disease Renal parenchymal disease Coarctation of the aorta Iatrogenic (medication, volume) Tumor History of Prematurity
1 to 6 years	Renal parenchymal disease Renovascular disease Coarctation of the aorta Tumor History of Prematurity
	Endocrine causes* Iatrogenic Essential hypertension
Age 6 to 10 years	Renal parenchymal disease Essential hypertension Renovascular disease Coarctation of the aorta
	Endocrine causes Tumor Iatrogenic
Adolescence, Age 12 to 18 years	Essential hypertension Iatrogenic
	Renal parenchymal disease Endocrine causes Coarctation of the aorta

**Shaded areas* are uncommon for category

Table 32.5 Relevant questions for the hypertensive history

Family history
Essential hypertension
Medications/diet control
Salt sensitive
Obesity
Systemic disease
Endocrine
Hyperthyroidism, diabetes
Obesity
Cardiovascular disease
Early myocardial infarction/stroke
Hyperlipoproteinemia
Kidney disease
Kidney failure, dialysis, or transplantation
Medications
Anti-inflammatory agents: steroidal and nonsteroidal
Decongestants
Stimulants: caffeine, Ritalin, Adderall
Antidepressants: tricyclics
Immunosuppression: cyclosporine, tacrolimus
Weight change
Weight loss or gain?
Weight loss as with pheochromocytoma
Weight gain as with exo- or endogenous steroids
Time frame for interval change in weight
Neonatal history: umbilical arterial catheter, neonatal asphyxia, bronchopulmonary dysplasia
Trauma
Systemic disease
Systemic lupus erythematosus
Polyarteritis
Flushing, sweating, headaches, palpitations as in pheochromocytoma, or neuroblastoma
Neurofibromatosis
Scleroderma
Urinary tract infections or history of unexplained or explained fevers
Substance abuse
Amphetamines

age group are unknown; however, the younger the patient and the more severe the hypertension, the more likely that the hypertension is secondary. 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. Renal or renovascular causes of hypertension account for ~90 % of secondary causes with 2 % contributed from abnormalities of the aorta and 0.5 % from pheochromocytoma [33, 34]. The National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (NHBPEP) has published a useful algorithm for childhood hypertension evaluation and management [2].

The personal and family history of hypertension and/or cardiovascular disease (Table 32.5) is a key starting point for the assessment of childhood hypertension; other important risk factors include meta-

bolic syndrome and sleep-disordered breathing (either from obstructive sleep apnea or snoring; see Chap. 27). Symptoms related to hypertension may be caused by the disease, related to the cause of the hypertension, nonspecific or absent. 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, cyclosporin or tacrolimus, corticosteroids, decongestants, performance-enhancing substances, caffeine, tobacco, and illicit drugs), congenital disorders, symptoms related to hypertension (headache, irritability), neonatal history (use of umbilical catheters, neonatal asphyxia), growth pattern, present and past history of kidney, or urologic disorders including urinary tract infections, symptoms suggestive of an endocrine etiology (change in weight, sweating, flushing, fevers, palpitations, muscle cramps), and family history of hypertension or other cardiovascular morbid or mortal events.

The physical examination should address direct attention to detecting causes of secondary hypertension (Table 32.6). In the majority of children with hypertension, however, the physical examination will be normal. For a child in the first year of life, secondary causes of hypertension are the rule, and even when no etiology is detected, secondary hypertension should

Table 32.6 Physical examination: clues to the etiology of hypertension

Body habitus
Thinness: pheochromocytoma, hyperthyroidism, renal disease (growth failure)
Short stature: renal disease
Obesity: Cushing disease, obesity-related HTN
Skin
Neurofibromas: neurofibromatosis
Malar rash: systemic lupus erythematosus café au lait spots–neurofibromatosis, tuberous sclerosis
Tubers, ash-leaf spots: tuberous sclerosis
Bruising: Cushing's disease, trauma
Rashes: vasculitis–collagen vascular disease, Henoch–Schönlein purpura or other vasculitis, or nephritic impetigo–acute nephritis
Striae: Cushing's disease
Needle tracks: drug-induced hypertension
Head and face
Unusual shape: mass lesion
Round facies (moon): Cushing's syndrome
Elfin facies: William's syndrome
Seventh nerve palsy: severe hypertension
Proptosis–hyperthyroidism
Neck
Goiter: hyperthyroid
Lungs
Rales, rhonchi: cardiac decompensation
Heart
Rub: chronic renal disease with hypertension
Abdomen
Masses: Wilms' tumor, neuroblastoma, hydronephrosis, polycystic kidney disease
Hepatomegaly: heart failure
Hepatosplenomegaly: infantile polycystic disease
Bruit: renovascular disease
Edema: renal/renovascular disease
Back/flank
Bruit: renovascular disease
Flank tenderness: pyelonephritic, obstruction, acute nephritis
Scoliosis: hypertension secondary to procedures
Pelvis
Mass: obstructive nephropathy, neuroblastoma
Genitalia
Ambiguous, virilized: congenital adrenal hyperplasia
Extremities
Disparity in BP, pulse, delayed refill: coarctation
Edema: renal insufficiency
Rickets: chronic renal disease

still be suspected (Table 32.4). In older children, by contrast, secondary hypertension has a different spectrum (Table 32.4). The physical examination should focus on symptoms and signs of hypertension (Table 32.6). For all age groups with hypertension, kidney disease is a common etiology where approximately 60–90 % is secondary to renal parenchymal or renovascular disease [33, 34]. Physical examination may reveal cranial (infants), neck, back, 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. Initial evaluation should also assess four extremity BP measurements to screen for coarctation of the aorta. Physical examination should include calculation of the body mass index (BMI) because of the strong association between obesity and hypertension.

The child with confirmed hypertension should be screened with laboratory testing and imaging to find identifiable causes, comorbid conditions, and ascertainment of end-organ damage. A serum creatinine and estimation of glomerular filtration rate (GFR) [Schwartz formula] [35] is also fundamental. The importance of a complete urinalysis with urinary protein or microalbumin and sterilely collected urine for culture cannot be overemphasized. Proteinuria or hematuria may be revealed and indicates possible glomerular disease or other nonglomerular conditions such as pyelonephritis, obstructive uropathy, and interstitial nephritis. Additional testing can be chosen by examining the individual and family history. A young child with stage 2 hypertension or in those with systemic symptoms should undergo a more extensive evaluation. On the other hand, the older or obese child with a significant family history of say diabetes or other cardiovascular risks will have a more streamlined approach for the metabolic abnormality.

A renal ultrasound is a simple and informative noninvasive test and appropriate for the initial screening. The prevalence of abnormalities revealed by a renal ultrasound may be low; however, the importance of findings and noninvasive nature makes it a valued screening test. The information provided can reveal asymmetrically sized kidneys, which would suggest vesicoureteral reflux, obstruction, unilateral infection, or possible kidney dysplasia—symmetrically enlarged kidneys indicating potential infective (pyelonephritis) or glomerular disease. Additionally the renal ultrasound easily documents renal calculi, nephrocalcinosis, renal parenchymal cysts, polycystic kidney disease, or 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 [36, 37], making other imaging studies frequently necessary (see below).

Serum electrolytes most commonly will be normal; however, alterations of potassium concentrations can indicate primary or secondary hyperaldosteronism, particularly when the potassium is low and there is a concomitant metabolic alkalosis. Liddle's syndrome, the syndrome of apparent mineralocorticoid excess, Gordon's syndrome, glucocorticoid remediable aldosteronism, and other forms of monogenic hypertension are often associated with this electrolyte pattern and altered renin and aldosterone levels (Fig. 32.2) [38]. By contrast, elevated potassium in conjunction with a metabolic acidosis may suggest

	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	β γ subunit of ENaC	16p	
Gordon's	AD	A (C)	N or↑	↓	N or↑	↑	-	-	T	WNK1/4	1q,12p13,17p	
AME	AR	I,C,A	↓ (N)	↓	↓		-	+	MR-A	11-β-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	11β-hydroxylase
CAH	AR	I	N or↓	↓	↓		-	+	MR-A	CYP11B1		
FGR	AR/AD	I	N or↓	↓	↓		-	+	MR-A			

Fig. 32.2 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 [52])

kidney disease. Indeed, this diagnosis may be supported by an elevation in serum creatinine or one may find nephrocalcinosis on renal ultrasound indicating a renal tubular defect.

b. *What are the consequences of the hypertension: end-organ damage?*

The relationship of hypertension to end-organ damage is critical to the true definition of hypertension and discussed in detail by Sorof [22]. The evaluation of hypertension is not solely to determine where 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. 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. Fundoscopy, typically reserved for patients with severe hypertension, rarely discloses hemorrhages or exudates, but many reveal arteriolar narrowing and arteriovenous nicking. 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. Daniels et al. using direct ophthalmoscopy showed 51 % of children with primary hypertension had retinal abnormalities [39]. More recently, 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 μm was seen in the retinal arterioles [40].

LVH is a clear and independent risk factor for cardiovascular morbidity and mortality in adult patients, but its significance is less clear for children unless it is severe and found to compromise cardiac function. The echocardiogram is more sensitive than the electrocardiogram for the determination of left ventricular hypertrophy/index [41]. ABPM has been shown to have a significant correlation to left ventricular mass

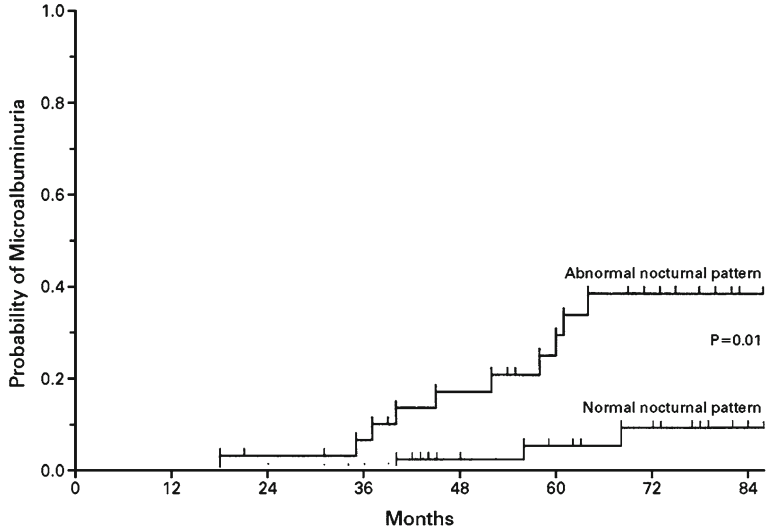

Fig. 32.3 Increase in nocturnal blood pressure and progression to microalbuminuria Kaplan–Meier curves showing the probability of microalbuminuria according to the pattern of daytime and nighttime systolic pressure. The probability of microalbuminuria differed significantly between the two groups ($p=0.01$ 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 [45]

index where casual BP measurements do not. Specifically the best predictors include the 24 h, wake or sleep mean BP, BP load, or BP index [22]. Additionally, further evidence for hypertension's role in causing end-organ damage in pediatrics emanates from the correlation of the carotid intimal-medial thickness and left ventricular mass index with hypertension and obesity [42]. There is a growing body of evidence which demonstrates an association with non-dipping status (failure of BP to decline with sleep) and an increased risk of adverse events (Fig. 32.3) [18-20, 23, 24, 43-45]. Additional markers of end-organ damage include elevated microalbumin excretion, which is especially important in diabetics, patients with CKD, and the obese as a marker of hypertensive end-organ damage**.** The presence of end-organ damage in a child is an absolute indication for pharmacologic treatment of hypertension [2].

With regards to the association of ABPM with end-organ damage for adults and children, those with WCH have a prevalence of end-organ damage not different from normotensive subjects. Conversely, those with masked hypertension have end-organ damage prevalence not dissimilar from children with sustained ambulatory hypertension [22, 46].

c. *What other risk factors for cardiovascular disease may be present?*

The major modifiable cardiovascular risk factors are hypertension, diabetes, smoking, hyperlipidemia, and proteinuria (chronic kidney disease) and should be evaluated during the initial screening process. A reasonable list of tests for cardiovascular risk assessment includes a fasting lipoprotein analysis including cholesterol; triglycerides; HDL, LDL, and VLDL; a fasting glucose and insulin for assessment of insulin resistance; microalbumin excretion; echocardiography; and kidney function. However, not all of these studies have been endorsed by consensus organizations for routine screening [2].

Phase 3: What is the definition of the abnormality?
Phase 3 evaluation is designed to further clarify and define abnormalities identified during Phase 2 in any of the three categories of etiology, risk factors, and end-organ damage determination. Concerning etiology, performance of stage 3 evaluation should be done for the very young hypertensive patient or for those with severe hypertension even if Phase 2 is unremarkable (Table 32.1).

At this point, we aim to find the abnormality but specifically limit 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, we might perform a thyroid panel but not for everyone. 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. Imaging studies provide information on the condition of the renal parenchyma and renovascular dysfunction. Renal ultrasound with Doppler flow analysis in conjunction with other studies can reveal the etiology for diagnosis of certain kidney lesions. 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}Tc dimercaptosuccinic acid (DMSA), ^{99m} Tc glucoheptonate (DTPA), or ^{99m} Tc mercaptoacetyltriglycine (Mag_3) and can be done with diuretics to help assess if the presence of hydronephrosis is obstruction. In children with a history of urinary tract infections and the diagnosis of vesicoureteral reflux or bladder abnormalities is entertained, voiding cystourethrography should also be performed. Detection of proteinuria requires either quantitation 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).

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) [46] or abdominal coarctation [47-49] or intracranial disease [50]. In our experience, Doppler ultrasound is very specific but insensitive test for renovascular hypertension. Screening for renal artery stenosis in children with captopril scans has also been unrewarding. Magnetic resonance angiography may become a valuable tool for detection of renal artery stenosis in children, but no large studies have yet validated the technology. It may be used as a screening test, but if there is a high index of suspicion, arteriography, the gold standard, should still be performed. Please see Chap. 24 for a more thorough discussion of these issues.

If other risk factors are identified, testing and/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. 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 abnormality
At this point, having found an abnormality, we now look for a test or series of tests that will provide information regarding the medical or surgical correctability of the problem. If a renal artery stenosis is detected by renovascular imaging, renal vein renins may provide further evidence for surgical correction. If an elevated serum metanephrine or urinary catecholamines is found suggesting a pheochromocytoma, then an octreotide or metaiodobenzylguanidine (MIBG) scan would aid in localization for surgical correction. A finding of significant proteinuria or hematuria with RBC casts would suggest that a renal biopsy be performed. This

information is also helpful in determining the type of antihypertensive therapy to be used. If abnormalities in serum renin or aldosterone consistent with the genetic syndromes outlined in Fig. 32.2 are found, specific therapies such as amiloride or spironolactone are suggested [51, 52]. Finding of CKD or diabetes can suggest the use of drugs affecting the renin-angiotensin-aldosterone system such as ACE inhibitors or angiotensin-receptor blockers.

Summary

While cardiovascular endpoints or the presence of hypertensive end-organ damage should be the basis for the definition of pediatric hypertension, this is not currently the case. Primary hypertension, as defined by BP measurements exceeding the 95th percentile for height with no underlying cause, is increasing in prevalence, particularly in older children and adolescents with hypertension risk factors, especially obesity. We recommend the evaluation of the pediatric hypertensive patient be performed in phases beginning with the confirmation of hypertension beyond the office measurement (Phase 1). This confirmation should be followed by the screening phase which further defines (a) the etiology of the hypertension knowing that younger patients are more likely to have a secondary etiology and older patient primary hypertension, (b) other risk factors for cardiovascular/kidney disease, and (c) hypertensive end-organ damage. Phase three defines the abnormalities in either a, b, or c, and the fourth and final phase is the determination of the significance of observed findings.

We recommend pharmacologic treatment of all children and adolescents with persistent hypertension due to the believed risk of end-organ damage and the lack of long-term efficacy of non-pharmacologic therapy as a sole therapy. Evidence-based definitions of pediatric hypertension and the indication for treatment are currently evolving as well as the introduction of new information for areas of pre- and postnatal causes of hypertension; genetics of hypertension; the relationship of obesity, diabetes, and CKD to hypertension; the use of ABPM in the evaluation of childhood hypertension; and the introduction of new pharmacologic therapy. Clearly, the information presented in this text has improved our understanding of the pathogenesis, diagnosis, and treatment of childhood hypertension; however, significant advances remain to be made. The most efficient tests and evaluation pathways for determining which children have secondary forms of hypertension or who are at risk for end-organ damage have also yet to be determined.

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The Role of ABPM in Evaluation of Hypertensive Target-Organ Damage

33

Empar Lurbe and Josep Redon

Abstract

Casual blood pressure measurement has provided the basis for the present knowledge of the potential risk associated with hypertension and has guided patient management for many years. The possibility of carrying out repeated ambulatory blood pressure measurements using automatic or semiautomatic devices allows for the gathering of more representative values of blood pressure and for observing the behavior of blood pressure during both moments of activity as well as rest. Ambulatory blood pressure measurement is now increasingly recognized as being indispensable to the diagnosis and management of hypertension, and it has contributed significantly to our understanding of hypertension. Likewise, the better relationship of ambulatory blood pressure measurements with the presence of organ damage and the prognosis to develop it have provided additional support to ambulatory blood pressure as a clinical valuable tool in the research, evaluation, and management of high blood pressure in children and adolescents.

Keywords

Children • Adolescents • Hypertension • ABPM • Target-organ damage

Introduction

The goal of blood pressure (BP) measurement in children and adolescents is to provide strategies for promoting cardiovascular health which should be integrated into a comprehensive pediatric health-care program. Blood pressure, however, is a parameter that changes on a beat-to-beat basis in response to a variety of physiological and environmental stimuli. Nevertheless, casual BP measurement has provided the basis for present knowledge of the potential risk associated with

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hypertension (HTN) [1] and has guided patient management for many years [2]. A few BP measurements obtained in the office, on the contrary, may not necessarily reflect the true BP of an individual. Subsequently, a better characterization of BP level and variability could lead to a better stratification of risk. This line of reasoning has led, consequently, to the development of methods that permit the acquisition of a large number of measurements under normal living conditions [3]. The possibility of carrying out repeated ambulatory BP measurements using automatic or semiautomatic devices allows for the gathering of more representative values of BP and for observing the behavior of BP during both moments of activity as well as rest [4]. Indeed, over the last few years, ambulatory BP monitoring has been introduced into pediatric populations, contributing to a significant increase in the bulk of knowledge of crucial clinically relevant issues [5].

Ambulatory BP measurement is now increasingly recognized as being indispensable to the diagnosis and management of HTN [6], and it has contributed significantly to our understanding of HTN by revealing or "unmasking" BP phenomena that were not readily apparent using traditional techniques of measurement in clinical practice. These have included the dipping and non-dipping patterns of nocturnal BP [7] and white-coat HTN [8] to which now must be added masked HTN [9]. Likewise, the better relationship of ambulatory BP measurements with the presence of organ damage and the prognosis to develop it have provided additional support to ambulatory BP as a clinical valuable tool in the research, evaluation, and management of high BP in children and adolescents [5].

The use of ambulatory BP monitoring is now recommended in several situations by the Fourth Report on the Diagnosis, Evaluation and Treatment in Children and Adolescents [10], the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee [11], and the Recommendations of the European Society of Hypertension [12] (Table 33.1). These documents have established the currently known conditions where ambulatory BP monitoring is useful and where it will provide additional information in children and adolescents. Aside from the assessment of refractory HTN or drug-induced hypotension, ambulatory BP monitoring is useful in the evaluation of white-coat and masked HTN and in target-organ injury risk. Furthermore, ambulatory BP monitoring gives additional BP information in chronic kidney disease, diabetes, and autonomic neuropathy. In these diseases, in which abnormal circadian variability is frequent and worsens the prognosis, ambulatory BP monitoring is the only method capable of assessing the absence of circadian rhythm on an outpatient basis.

Table 33.1 Recommendations for 24-h ambulatory BP monitoring

During the process of diagnosis
Confirm hypertension before starting antihypertensive drug treatment
Type 1 diabetes
Chronic kidney disease
Renal, liver, or heart transplant
During antihypertensive drug treatment
Evaluation of refractory hypertension
Assessment of BP control in children with organ damage
Symptoms of hypotension
Clinical trials
Other clinical conditions
Autonomic dysfunction
Suspicion of catecholamine-secreting tumors

Ambulatory Blood Pressure Monitoring in the Diagnosis

Since pediatricians agree on operational thresholds, ambulatory BP monitoring has become an established instrument for the diagnosis of HTN in children and adolescents [13, 14]. By using not only office but also ambulatory BP, four possible situations arise. Two of these have values in agreement for normotension or HTN. Two have values that are discrepant. The latter two are known as white-coat and masked HTN. In sustained normotension or HTN, both office and daytime ambulatory BP were normal and elevated, respectively. White-coat HTN is the transient elevation of a patient's BP in response to the

Table 33.2 Association of ambulatory blood pressure with hypertension-induced organ damage of white-coat and masked hypertension in children and adolescents

Author	Population characteristics	Prevalence white coat	Prevalence masked	Association TOD
Sorof [16]	71 referred subjects	31 %	–	–
Matsuoka [19]	202 normo-hypertension	47 %	–	–
Matsuoka [24]	138 normo-hypertension	–	11 %	–
Lurbe [17]	592 population study	1.7 %	7.6 %	LVH in masked
Stabouli [18]	85 referred subjects	12.9 %	9.4 %	LVH in masked
McNiece [20]	163 referred subjects	Stage 1–34 % Stage 2–15 %	20 %	LVH in masked
Kavey [21]	119 referred subjects	52 %	–	LVH in white coat
Lande [22]	217 referred subjects	31 %	–	–
Stergiou [23]	102 referred subjects	18 %	11 %	–
Mitsnefes [29]	366 CKD subjects	–	38 %	LVH in confirmed and masked HTN
Di Salvo [30]	76 aortic coarctation repair	–	47.4 %	LVH in masked HTN

TOD target-organ damage, *LVH* left ventricular hypertrophy, *HTN* hypertension, *CKD* chronic kidney disease

observer measuring the BP [15, 16]. It has been characterized by a normal daytime ambulatory BP yet with elevated office BP. The opposite phenomenon, masked HTN, consists of elevated daytime or awake ambulatory BP with normal office BP [17].

Besides the fact that there was different mean ambulatory BP than office BP in the individual patient, the discrepancies have clinical relevance. How common and important the intraindividual differences are within clinical and ambulatory BP is the keystone to the use of ambulatory BP monitoring as a diagnostic tool. The prevalence and significance of the two discrepant conditions, white-coat HTN and masked HTN, are not well understood and differ according to the characteristics of the subjects analyzed. The main studies in the prevalence and significance of white-coat and masked HTN in children and adolescents are shown in Table 33.2.

White Coat

The prevalence of white-coat HTN, the first of the two discrepant conditions to be recognized, differs largely among the studies published, ranging from very low values to very high as much as 44 % [16], since it depends not only on the threshold selected to define HTN by using ambulatory BP values but also on the population included and the procedure of office BP measurements.

The elevated figures for the white-coat phenomenon are dependent at least in part on the defining threshold for the upper limit of normality for ambulatory BP. The higher the ambulatory BP threshold, the greater the white-coat phenomenon is. Sometimes the thresholds used are the same for both ambulatory as well as for office BP. If not, they have been selected comparing age- and height-based reference values for office BP with height-based values for ambulatory BP. Another factor is the kind of population included. Sorof et al. [16] and Stabouli et al. [18] in two studies, which included children referred to a HTN clinic, reported that white-coat HTN was present in 44 and in 12.9 % of the subjects, respectively. Other studies also performed in referred subjects had figures in within the previously mentioned [19–23]. In contrast, one study which included healthy children and adolescents diagnosed only 1 % to have white-coat HTN [17]. This very low prevalence was dependent not only on the kind of population studied but also on the method used to assess the office BP values, since BP status was qualified using the average of three measurements, and office BP was measured by nurses which reduce the potential for alarm reaction.

Concerning the significance of white-coat HTN, children with white-coat HTN tended to have a higher left ventricular mass index (LVMI) than confirmed normotensives did, although no significant differences were observed between the groups [16, 18, 20]. Furthermore, there are currently no data on the long-term follow-up of children found to have white-coat HTN upon initial assessment, and questions concerning reproducibility of the phenomenon and whether the white-coat phenomenon in adolescents is an innocuous phenomenon or a prelude to future permanent adult HTN need to be clarified. Thus, there is presently insufficient evidence in children to assert that normal ambulatory BP in conjunction with a persistently elevated casual BP is necessarily reassuring.

Masked

The opposite phenomenon, the so-called masked HTN, occurred in approximately 10 % of children and adolescents in studies which have explored this condition [17, 18, 23], although higher prevalence has been reported in other, 22 % [20]. Key issues such as the persistence and the significance of the phenomenon were analyzed in a prospective study [17]. Follow-up of 234 adolescents demonstrated that the abnormal elevation of the daytime ambulatory BP persisted in nearly 40 %. Furthermore, 1 out of 10 subjects with masked HTN is predisposed to the development of sustained HTN and has a higher left ventricular mass index with a prevalence of LVH of 22 % [20] and 10 % [24].

Adolescents with persistent masked HTN were more than twice as likely to have a parental history of HTN. Other characteristics observed in those with masked HTN were that they had a higher ambulatory pulse rate and body mass index than did normotensive subjects. These three characteristics, alone or in combination, predispose subjects to the development of HTN and an increase in cardiovascular risk later in life [17]. Parental history of HTN, tachycardia, and high body mass index are usually accompanied by stimulation of the sympathetic nervous system, which together with the elevated daytime BP and obesity might underlie the development of left ventricular hypertrophy in youth with masked HTN even before its preceding to sustained HTN [25, 26].

Because both HTN and LVH are harbingers of adverse cardiovascular outcomes later in life [27, 28], masked HTN in childhood should be regarded as a condition that requires further follow-up and intervention in whom this disorder persists. From a therapeutic point of view, masked HTN in pediatric patients is an indicator for further follow-up and the institution of lifestyle measures, which promote cardiovascular health and have the potential to decrease BP or delay the development of HTN. Once persistent for 1 year, masked HTN may be an indication for BP lowering treatment especially in children and adolescents with a positive family history of HTN. Whether pharmacological treatment should be initiated in such cases must await supporting evidence.

In a cross-sectional study of BP and cardiac structure in a large population of children with chronic kidney disease (CKD), LVH was strongly associated with HTN [29]. The presence of LVH was four times higher in children who were identified as having masked HTN compared with children with normal office and ambulatory BP. Likewise in patients with repaired aortic coarctation, there is a high prevalence of masked HTN, 47.4 % [30], which is associated with abnormal left ventricular structure and function.

As for the existence of white-coat or masked HTN in children, its importance as a clinical entity will depend on whether it carries risk for future cardiovascular outcome. Despite the scarce information available, recent research has added essential information that can help in the better design of future studies to answer practical questions and delineate clinical recommendations. The superiority of ambulatory over office BP underlines the diagnostic complement of ambulatory monitoring to conventional BP measurement at the office. Furthermore, Mancia and coworkers [31] established that each BP elevation (office, home, or ambulatory) carries an increase in risk mortality that adds to that of the other BP elevations. If the three, office, home or ambulatory, show normal BP values, the risk is lower compared to subjects that have at least one of the

three BPs elevated. If the elevation exists in two, the risk is even higher. Furthermore, if the three BPs are elevated, the risk is the highest.

Masked HTN in children presents pediatricians with the serious problem of identifying subjects with the condition. This gives rise to a very pertinent question. Which children need ambulatory BP monitoring? Although the question has yet to be resolved, ambulatory BP monitoring is useful not only for stratifying risk in individual subjects but also for providing data which will add to our knowledge of this issue. Clearly, it is not practical to perform ambulatory BP monitoring in all subjects with normotension in the office or clinic to unmask those with ambulatory HTN, but we have to face the reality that children with masked HTN may be seriously disadvantaged if ambulatory BP monitoring is not performed. Once masked HTN is detected, repeated office BP measurements should be encouraged to detect the potential progressive rise in BP values.

Clinical Significance of Discrepant Phenomenon

The occurrence of white-coat HTN and the reverse phenomenon of masked HTN in at least 10 % of children and adolescents introduce the potential for misdiagnosing subjects who present themselves to doctors for BP measurement. This estimate, which is conservative, must surely make ambulatory BP monitoring an indispensable research tool for the diagnosis and management of HTN in children and adolescents [32], mainly in those at higher risk. The finding that masked and white-coat HTN occur in at least 10 % and 21 % of the moderate and severely obese, respectively, emphasizes the likelihood of misdiagnosing clinically relevant BP problems in obese youths [33].

Ambulatory Blood Pressure Monitoring and Hypertension-Induced Organ Damage

Once HTN is confirmed, organ damage evaluation should include heart, great vessels, and kidney due to the importance of subclinical organ damage as an intermediate stage in the continuum of vascular disease. Cardiovascular damage develops in parallel to renal damage, although the cardiovascular sequelae of childhood onset HTN, such as LVH and dysfunction and atherosclerosis, may not become clinically relevant before adulthood. Subsequently, evaluation of organ damage is also useful as an intermediate end point for monitoring treatment-induced protection.

Ambulatory BP monitoring has provided knowledge about the role of the BP components on the development of HTN-induced organ damage. Hypertension in children as defined by casual BP values, however, is not well correlated to any particular form of hypertensive target-organ damage. Ambulatory BP monitoring may overcome these limitations; therefore, ambulatory BP monitoring became an established instrument for the evaluation and prognosis [5] due to the ability to obtain more accurate and reproducible BP values [13] and the estimation of circadian variability [34], a parameter that had demonstrated additional value in the evaluation of HTN and its impact in organ damage.

Renal Diseases

Renal disease in children is frequently associated with high BP. An increase in BP as a consequence of kidney disease contributes to the progression of renal damage. A rapid progression of renal damage may result in end-stage renal insufficiency during childhood. Cardiovascular damage develops in parallel to this, although the cardiovascular sequelae 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 which progresses to end-stage renal disease. 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 ambulatory BP values in the progression of renal disease has come from several clinical studies in children with or without established renal insufficiency.

Besides the GFR reduction, an increase in urinary albumin excretion is a marker of HTN-induced renal damage. Proteinuria is a marker of glomerular damage in primary and secondary glomerulopathies that can increase as a consequence of elevated BP values, so it should be targeted by lowering BP. Even small amounts of urinary albumin excretion (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 organ damage associated with a subtle increase in UAE. The role of microalbuminuria assessment in pediatrics, however, is limited to diabetics.

The regular use of ambulatory BP monitoring in patients with renal disease not only permits a better assessment of BP control but also frequently uncovers circadian variability abnormalities. A blunted nocturnal BP fall, the non-dipper pattern, is characteristic for renal failure, whichever the etiology. The role of the pattern as either a marker or a pathogenic factor for kidney damage has been stressed in many studies [35].

Patients with a decrease in glomerular filtration rate (GFR) are likely to show less of a nocturnal dip in BP and frequently show an increase in nocturnal versus daytime BP levels when these are compared with the BP profiles from normotensives or hypertensives with a normal GFR [36–38]. The prevalence of non-dipping rises, however, with worsening renal function, reaching statistical significance once plasma creatinine is elevated to levels greater than 400 μmol/l [34]. When GFR decreases to extremely low levels of <10 ml/min and creatinine reaches values greater than 600 μmol//l, more than 70 % of these end-stage renal disease subjects show the non-dipper pattern. This figure is practically the same as that seen in patients during renal replacement therapy. After renal transplantation, an abnormal BP decline in nighttime occurs almost universally in adults as well as in children [39–44]. Some of these patients may experience reverse dipping, with nighttime BP exceeding daytime BP. In a study by Sorof et al. [42], 72 % of the 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 [45], reflux nephropathy [46, 47], and type 1 diabetes [48]. It is from the last disease where the greatest of amount information has been obtained. The spectrum of abnormalities of circadian BP variability through all the nephropathy stages of type 1 diabetes shows about 58 % of the microalbuminuric and 80 % of the proteinuric subjects have a persistently blunted BP fall during the night. The reduction in the BP nocturnal fall is independent of the disease duration [49]. In type 1 diabetes, the presence of persistent microalbuminuria represents an early BP dysregulation during sleep even in the absence of HTN. When overt nephropathy is established, HTN is present and abnormalities in the circadian BP profile are more conspicuous. A pathogenic role of nocturnal systolic BP has been related to the development of microalbuminuria in normotensive type 1 diabetics [50]. An increase in BP during sleep precedes the development of microalbuminuria, whereas in those whose BP decreased normally during sleep, the progression to microalbuminuria was less frequent.

Mechanisms underlying the circadian variation abnormality are not well understood. No potential role of sympathetic overdrive was found in a study comparing plasma norepinephrine values in dipper and non-dipper end-stage renal disease subjects [51]. Some authors affirm that the presence of the non-dipper pattern in subjects with end-stage renal disease depends on the presence of autonomic neuropathy or corticosteroid treatment rather than on the end-stage renal disease itself [52], although the prevalence of non-dipper pattern increases with further decreases in GFR.

Whether the abnormal circadian variability may contribute to further kidney damage is a matter of debate. Some evidence supports the potential role of systemic BP transmission as a mechanism of inducing renal damage, whereas other evidence supports the non-dipping pattern as a consequence of the renal damage itself. Neither the cause nor the consequence interpretations of these data are mutually exclusive. In some cases, higher BP values during nighttime may contribute to the progression toward renal

insufficiency, while in other cases the values are but 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 HTN.

There is practical utility associated with the assessment of circadian variability. First, it 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 HTN can 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 consistently above the 95th percentile for age, sex, and height have determined the need to initiate antihypertensive treatment in children and adolescents [10]. Nevertheless, the presence of a non-dipping pattern, when BP values are below the 95th percentile, has not been deemed a sufficient cause to start treatment. Future studies need to be conducted to address this specific point.

The utility of ABPM in establishing the goal of BP values to protect the kidney in children and adolescents with CKD has been demonstrated in the ESCAPE trial. The study was conducted in patients with different glomerular and interstitial nephropathies. The long-term renoprotective effect of intensified BP control (with a target 24 h mean arterial BP below the 50th percentile) or conventional BP control (in the 50–95th percentile) was assessed. Intensified BP control with target 24 h BP levels in the low range of normal confers a substantial benefit in reducing the risk to develop end-stage renal disease among children with CKD [53].

Heart

The abnormal increase of left ventricular mass (LVM) and/or geometry has been recognized as one of the most important markers of risk for HTN-induced cardiovascular morbidity and mortality in adults. In children and adolescents, the relationship 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 made by BP [54, 55]. The important contribution of the somatic growth and the recognition that lean body mass contributes somewhat more to cardiac growth than fat mass were nicely demonstrated in the Bogalusa Heart Study [56]. In a longitudinal study, LVM tracks from early to late adolescence to about the same degree as other important risk factors, such as BP and cholesterol [57]. Recently, the potential role of adiposity in the increment of LVM has been highlighted. Adiposity and LVM are related in childhood, and this association tracks and becomes stronger in young adulthood. Moreover, the increase in LVM from the child to the young adult is related to the degree of increase in body mass index [58].

Studies of normal and hypertensive children 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 left ventricular mass index. Sensitivity and response to hemodynamic load seems to vary with age, sex, and ethnicity, which explains some of the differences among published results.

Although epidemiological studies do not help to establish the difference between appropriate and excessive increases in LVM, operational thresholds have been established. Both the allometric definition of excessive mass (>51 g/m^2) and the percentile distribution of mass and geometry have been recommended. Using these operational thresholds, a few studies have analyzed the prevalence of LVH in not only healthy but also hypertensive children and adolescents. In hypertensive children, the prevalence of LVH ranges from 24 % to 40 % in different pediatric studies [59–62], Table 33.3.

The relationship between LVMI and systolic BP is more evident when BP is measured using 24 h ambulatory BP monitoring [62–67]. Consequently,

Table 33.3 Relationship between ambulatory BP and left ventricular mass index (LVMI)

Author	Study population number (condition)	Age (years)	Relationship
Belsha [63]	69 (normotensive, essential HTN)	10–18	Night-SBP
Hauser [64]	95 (aortic coarctation)	6–21	Day-SBP
Rucki [65]	108 (essential HTN)	8–20	Day-SBP
Sorof [62]	37 (referred for diagnosis of HTN)	9–17	24 h, day, night-SBP
Richey [66]	106 (referred for diagnosis of HTN)	6–18	24 h-SBP
Stabouli [67]	124 (referred for diagnosis of HTN)	5–18	24 h, day, night-SBP

HTN hypertension, *SBP* systolic blood pressure

hemodynamic load seems to play a more important role in the growth of LVM than previously recognized by using office BP. According with this, LVM tends to be greater in those groups with a higher ambulatory BP. In one cross-sectional study, both subjects with sustained HTN and masked hypertensives had significantly higher LVMI than confirmed normotensive [20]. Moreover, in a group with adolescents who had sustained masked HTN, LVMI was significantly higher than that observed in normotensive adolescents [17].

Vessels

Hypertension-induced abnormalities in arterial structure and function are important because they underlie many adverse effects. Assessment of vascular damage, however, received little attention prior to the advent of the advanced ultrasound technology which permits noninvasive study of vascular walls and lumen. Intima-media thickness measurement at the carotid artery is the most common of the methods to assess structural abnormalities. Since age and sex influence the values of intima-media thickness [68], 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 of intima-media thickness compared to those of normotensive controls [60, 69, 70], although one study did not observe differences among normotensives, white-coat, masked, or sustained hypertensives [18]. Moreover, a relationship between intima-media thickness and endothelial function has been established in the Cardiovascular Risk in Young Finns Study [71]. The impact of other cardiovascular risk factors besides HTN, such as cholesterol levels or smoking, needs to be considered in the interpretation of intima-media thickness levels, since these have been associated with intima-media thickness as well [72]. Moreover, measurement is not trivial and subject to some observer bias. Hence, despite the increasing evidence for its predictive value in cardiovascular disease, carotid intima-media thickness assessments have not yet been recommended universally for routine clinical use [10, 12].

The information about the relationship between carotid wall thickness and ambulatory BP is scarce and mainly performed in obese children. While one study provided strong evidence that carotid intima-media thickness is increased in childhood primary HTN independent of the effect of obesity [73], recent findings have demonstrated that obese children and adolescents have greater carotid intima-media thickness than nonobese subjects independent of BP [74]. These findings suggest a possible role of childhood obesity in the early onset of carotid artery atherosclerosis.

Conclusions

Ambulatory BP monitoring is now increasingly recognized as being indispensable to the diagnosis and management of hypertension. The superiority of ambulatory BP values over those of office BP, in relation to the presence and development of organ damage, supports the utility of this method in this age group. Therefore, it may contribute to a more refined approach to the reduction of cardiovascular and renal risk.

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Blood Pressure, Hypertension, and Exercise

34

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Abstract

Control of blood pressure during activity is a complex process. In this chapter, the physiologic response to activity in normal children and adolescents is reviewed. The exercise BP response and exercise testing recommendations in selected pediatric subpopulations are described: children with hypertension, children at identified risk for premature atherosclerotic disease, and individuals with relevant congenital heart diagnoses (aortic valve stenosis, coarctation of the aorta, hypertrophic cardiomyopathy). The evidence for exercise as nonpharmacologic treatment of primary hypertension is reviewed. This chapter ends with a description of existing activity recommendations for hypertensive children and adolescents.

Keywords

Hypertension • High blood pressure • Pediatric • Child • Activity • Exercise • Exercise recommendations

Normal BP Response to Exercise

In normal children, the physiologic blood pressure response to exercise is complex, involving increases in stroke volume and heart rate, changes in peripheral resistance, and a response to sympathetic output. Physiologic changes vary with the type of exercise with dynamic exercise, the increase in cardiac output is accompanied by a continuous steep rise in heart rate and systolic blood pressure, a small decrease in diastolic blood pressure, and a significant decrease in systemic vascular resistance [1–5]. The rise in systolic BP is higher in boys than in girls and increases in both sexes with increasing age and body size [2]. Both lean body mass and fat mass are important hemodynamic determinants of exercise blood pressure [6]. Consistent racial differences in the BP response to dynamic exercise have not been reported [7]. With treadmill exercise testing, systolic BPs as high as 250 mmHg have been recorded in healthy normotensive adolescent males.

With static or isometric exercise, there is an abrupt increase in both systolic and diastolic BP, a modest increase in heart rate, stable or limited decline in stroke volume, a small increase

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in cardiac output, and no change in systemic vascular resistance [4, 8–10]. The increase in systolic and diastolic BP with static exercise can be marked. In young adult male weight lifters, extremely high blood pressures, exceeding 400/300, have been reported from direct intra-arterial recordings [11].

BP Measurement with Exercise Testing

The role of exercise testing in the evaluation of children and adolescents with defined cardiac problems and in those with potentially cardiac symptoms continues to increase. Current guidelines from the American Heart Association published in 2006 review the equipment requirements, exercise protocols, and required measurements for safe and effective assessment of exercise performance in the pediatric age group [12]. Blood pressure responses to exercise testing have been reported for both bicycle ergometer and treadmill exercise testing in a variety of populations [2–5, 7, 13–27], with exercise blood pressures monitored manually or with automated instruments. The use of varying protocols makes direct comparison of these results difficult.

Regardless of the protocol or equipment, systolic BP rises continuously with dynamic exercise, with the difference from baseline to peak exertion increasing as age and body surface area increase. By contrast, diastolic pressure is stable or decreases slightly during exercise. Upper versus lower extremity blood pressure gradients with exercise testing have been evaluated in normal children and adolescents and are very small: mean arm-leg gradient at rest was −5 mmHg, increasing to 4, 2, and 1 mmHg at 1, 3, and 4 min postexercise [28]. In adults, a maximum normal systolic BP response to exercise testing is defined as 220 mmHg. However, measurement of BP response with radial artery catheterization in adults during exercise testing revealed that direct systolic BP was significantly greater than cuff systolic BP by a mean of 29 mmHg with maximal exercise systolic BP exceeding 240 mmHg in 20 % of subjects [29]. Defining the normal maximum BP response to exercise in adolescents has been challenging, with cuff systolic BPs as high as 250 mmHg being recorded in studies of normotensive postpubertal male athletes [2, 30]. The AHA guidelines state that "… there is no evidence of danger when the systolic blood pressure reaches the 250 mmHg range during exercise in an asymptomatic child or adolescent" [12].

BP Response to Exercise in Pediatric Subpopulations

Children and Adolescents with Hypertension

The BP response to exercise correlates best with resting BP and this is true across the BP distribution in normal children and in those with hypertension [4]. For children with hypertension, the change in SBP and DBP with dynamic and isometric exercise is similar to that seen in non-hypertensive subjects, but BPs are higher, paralleling those of normotensive children at a higher level [30–35]. With effective treatment, exercise BP decreases in parallel with changes in office and ambulatory BP. The 2005 Bethesda Conference recommendations on competitive exercise in individuals with cardiovascular disease address systemic hypertension without distinguishing children and adolescents from adults [36]. The BP-lowering effects of repetitive exercise are reviewed and regular dynamic activity is recommended. Intensive resistive training is not recommended. Athletic participation is limited only "until BP is controlled by appropriate treatment." The American Academy of Pediatrics Council on Sports Medicine and Fitness released new recommendations for athletic participation by children and adolescents with systemic hypertension in 2010 [37]. Daily physical activity is recommended regardless of BP status. Individuals with prehypertension or grade one hypertension are not limited from participation in competitive athletics. Youth with stage two hypertension are restricted from competing in high-static sports until BP is in the normal range. Other expert commentaries have also recommended routine dynamic exercise and no exercise limitation in hypertensive children and adolescents on therapy [30, 38–40].

Children at Increased Risk for Future Hypertension and/or Cardiovascular Disease

In normotensive adults, an exaggerated BP response to exercise testing has been shown to predict future hypertension and increased cardiovascular risk and to correlate with increased arterial stiffness and impaired endothelial function [41–44]. In children, the predictive value of exercise BP has also been evaluated. From 3.4 years of follow-up in the Muscatine study, subsequent systolic BP was best predicted from initial resting blood pressure, maximal exercise systolic BP, and left ventricular mass. Only exercise blood pressure effectively predicted subsequent LV mass [45]. In normotensive adolescents, systolic BP response to exercise was significantly higher in those with a family history of hypertension than in controls [46]. In 7–10-year-old boys with a family history of premature myocardial infarction, a significantly greater systolic blood pressure and total peripheral resistance was demonstrated in response to cycle ergometer testing [47]. In a larger group from the same laboratory, 1-year stability was demonstrated for dynamic pressor responses in children from hypertensive families [48]. Evaluation of the pressor response to treadmill exercise in 6–7-year-old black and white children showed that stress responses are predictive of resting cardiovascular function at 2.5-year follow-up [49]. In a study of Dutch adolescents and young adults, exercise responses to isometric exercise and bicycle ergometry were compared in those with two hypertensive parents and those with normotensive parents. Offspring of hypertensive parents were found to have increased total peripheral resistance during isometric exercise and an attenuated increase in stroke volume with dynamic exercise [50]. In a small series of boys with severe hypercholesterolemia, exercise systolic and diastolic blood pressures were found to be significantly higher than in normolipidemic controls suggesting altered control of arterial vascular tone in this setting [51]. Among children and adolescents with white-coat hypertension defined by elevated office blood pressures with normal ambulatory BP recordings, 38 % had an exaggerated BP response to treadmill exercise, compared with 63 % of those with sustained hypertension. This was felt to suggest that white-coat hypertension in childhood may represent a true prehypertensive state [35]. In a cross-sectional study of Danish third and ninth graders, systolic BP measured during a maximal aerobic fitness test correlated significantly with other cardiovascular disease risk factors including BMI and insulin resistance [52]. In summary, the BP response to exercise appears to be exaggerated in children who are at increased risk for hypertension and early atherosclerotic disease.

Congenital Heart Disease

There are three congenital cardiac diagnoses in which the blood pressure response to exercise has been extensively evaluated: postoperative coarctation of the aorta, aortic stenosis, and hypertrophic cardiomyopathy. The characteristic exercise BP responses are summarized below.

Coarctation of the Aorta

After surgical repair of coarctation of the aorta, long-term follow-up studies document persistent hypertension, significant cardiovascular morbidity, and premature mortality despite elimination of resting arm-leg pressure gradient [53–55]. An upper body hypertensive response to exercise and development of a significant arm-leg gradient have been well described in these patients, even when resting blood pressures are normal [56–59]. Exercise-induced hypertension has also been reported after stenting of coarctation [60]. This has been attributed to a variety of mechanisms including histologic and physiologic abnormalities of the aortic wall [61], altered baroreceptor function [62], increased vascular resistance and abnormal vasodilator function in the upper body [63], increased norepinephrine response to exercise with increased plasma renin levels [64, 65], altered flow around the surgically altered aortic arch [66], and altered mechanics at the repair or stent site [67]. The significance of isolated exercise hypertension in post-coarctectomy patients

and its relation to clinical outcome is not known and some have suggested that exercise testing results in this context are not meaningful [68]. However, exercise-induced hypertension with normal rest pressures has been shown to correlate with increased carotid intima-media thickness, a subclinical measure of atherosclerosis, suggesting that it may contribute to the ultimate development of clinical cardiovascular disease [69]. In addition, exercise-induced hypertension with normal rest pressures has been shown to predict development of chronic hypertension in adults post childhood coarctation repair after a mean follow-up period of 6.3 years [70]. In the context of known increased risk, the presence of exercise-induced hypertension, especially if associated with increased LV mass, may identify a group of post-coarctectomy patients who warrant antihypertensive treatment. Cardioselective beta blockade has been shown to be effective in this setting [71].

Aortic Stenosis

As might be anticipated with obstruction to left ventricular outflow, the exercise response of patients with aortic stenosis is often abnormal. In adult series, the increase in cardiac output with exercise is reduced, approximately 50–60 % of normal [72, 73]. With exercise testing, this is associated with a blunted blood pressure rise, the development of anginal or pre-syncopal symptoms, and the onset of significant ST depression in one third to two thirds of asymptomatic adult patients, with abnormal results correlating best with resting gradient [74]. Several recent prospective series have shown that in asymptomatic patients, an abnormal exercise test is strongly predictive of an adverse outcome (the onset of clinical symptoms in daily life, aortic valve surgery, or sudden death) over relatively short-term (12–36 month) follow-up [75–79]. In Europe, exercise testing has been recommended to aid in clinical decision-making in asymptomatic patients with moderate gradients every year and with severe gradients every 6 months [80]. In the 2008 ACC/AHA guidelines for management of aortic valvular disease, exercise testing is recommended in asymptomatic adults with moderate Doppler gradients above 50 mmHg [81].

In children with aortic valve stenosis, exercise results have been less consistent. Beginning in the 1960s, characteristic ischemic ECG changes of ST-segment depression with exercise were reported in children with aortic valve stenosis; the presence and severity of the ischemic response correlated with the magnitude of the aortic valve gradient [82–84]. In the 1970s, a series of investigators reported lower systolic BP rise with exercise in children with aortic stenosis compared with normal children and suggested that the exercise BP response, combined with analysis of electrocardiographic changes, could be used to quantify the severity of stenosis [85–87]. However, in one of the largest series, 70 children with isolated AS, maximal exercise responses for work load, heart rate, and peak working capacity were reduced compared with normal controls, but neither maximal blood pressure response nor ECG abnormalities correlated with the severity of the outflow gradient [88]. Unfortunately, there was no physiologic measure of exercise effort to validate comparison among the patients with aortic stenosis and controls. A later report of exercise testing during cardiac catheterization demonstrated that aortic stenosis patients with exercise-induced ST-segment depression had significantly higher exercise LV pressure, higher LVOT gradient, and lower aortic systolic BP with a correspondingly higher LV-O2 supply/demand ratio, supporting the concept of myocardial ischemia as the etiology of electrocardiographic findings [89]. Two more relatively recent studies have demonstrated a greater increase in QT interval with exercise in patients with AS compared with controls and this has been suggested as a potential mechanism for rare cases of serious ventricular arrhythmias and sudden death in this population [90, 91]. Finally, a recent survey-based review of current practice among academic pediatric cardiology programs in managing patients with aortic stenosis reported that 28 % of programs use exercise testing including BP response as part of the routine evaluation and follow-up of children with moderate and severe aortic stenosis [92]. The most recent Bethesda Conference guidelines on competitive athletics in children with heart disease require

exercise testing results in patients with moderate aortic stenosis to determine exercise recommendations [93].

Hypertrophic Cardiomyopathy

Sudden death is a dreaded occurrence in patients with hypertrophic cardiomyopathy (HCM) and the risk is greatest in children and young adults [94–102]. Exercise hypotension has been well documented in this setting, occurring in approximately a third of patients, and is strongly associated with young age and a family history of sudden death [103]. In prospective studies from both tertiary referral centers and community-based populations, an abnormal BP response to exercise was observed in 11–37 % of patients. On follow-up, an abnormal BP response to exercise is associated with increased risk of sudden cardiac death with high negative but low positive predictive accuracy [104–106]. The pathophysiologic basis for failure to increase blood pressure appropriately during exercise has not been definitively identified [107–110]. Recent evidence-based guidelines addressing diagnosis and treatment of HCM from the American College of Cardiology/European Society of Cardiology [111] and the American College of Cardiology Foundation/American Heart Association [112] recommend upright exercise testing using a Bruce or modified Bruce protocol and defined an abnormal BP response as <20 mmHg rise in systolic BP from baseline or >20 mmHg decrease in systolic BP from peak in the first minute postexercise as abnormal. A normal BP response helps to define a low-risk patient; an abnormal BP response requires further risk stratification. In addition to the abnormal hemodynamic response, exercise testing can elicit ventricular arrhythmias; while rare, this is associated with increased risk of sudden cardiac death [113, 114].

Since the second edition of this text, there has been an increased focus on exercise-echocardiographic assessment of patients with HCM for development of left ventricular outflow tract gradients [112, 115–118]. In patients with no significant rest gradient, demonstration of a postexercise gradient >30 mmHg is said to redefine the HCM as obstructive. A history of syncope or pre-syncope independently predicts development of a significant postexercise outflow tract gradient. The recent ACC/ESC and ACCF/AHA guidelines recommend exercise echocardiography for the detection and quantification of dynamic LVOT obstruction in patients with a resting echo/Doppler gradient of less than 50 mmHg [111, 112]. In HCM, outflow tract obstruction at rest is clearly associated with a worse prognosis, but the prognostic significance of exercise-provoked gradients in adults is unclear and this has not been assessed in children or adolescents. In a retrospective review of exercise test results and survival over a 4-year follow-up in minimally symptomatic adults, lower BP response to exercise, higher LV outflow tract gradient at rest, and lower peak oxygen consumption were significant predictors of death or severe symptoms [119].

While most of the studies reported above have included children and adolescents, there have been some that exclusively evaluated children with hypertrophic cardiomyopathy. In a small series from Japan, exercise BP response was reduced in all ten patients with HCM and two had a hypotensive response to exercise [120]. A series of 23 patients with HCM, aged 6–23 years, with previous history of cardiac arrest, syncope, or a family history of sudden cardiac death underwent exercise thallium scintigraphy, electrophysiologic study, and ambulatory ECG monitoring [121]. In this highly selected patient group, all patients with a history of syncope or cardiac arrest had inducible ischemia on thallium scintigraphy and a majority had LV cavity dilation. BP response to exercise is not reported. In a continuous series of 99 pediatric patients with HCM, all less than 18 years of age, treadmill exercise results were reported in 43 [122]. All patients survived testing, but 42 % had a hypotensive response to exercise and 19 % developed chest pain with significant ST depression. Unfortunately, exercise results were only available for one of the subset of 12 patients from the whole series who went on to sudden death; in that child, there was a BP drop with exercise. A consecutive series of children with HCM were evaluated by echocardiography, ambulatory ECG monitoring, and exercise testing [123]. Of the 38

children who underwent exercise testing, 16 were symptomatic and 50 % of these had a blunted BP response to exercise, compared with 10 % of asymptomatic children. Maximum oxygen consumption (VO2max) was significantly lower in the symptomatic patients, and by linear regression, there was a significant inverse relationship between NYHA class and VO2max. Children with HCM had significantly decreased early diastolic tissue Doppler velocities for ventricular inflow compared with controls and in regression analysis, early transmitral left ventricular filling velocity predicted death, cardiac arrest, or ventricular tachycardia. Maximum oxygen consumption with exercise was most predictive of subsequent symptomatology. In an extension of this study, a restrictive physiology pattern, defined as either left atrial enlargement without left ventricular dilation, abnormal early diastolic tissue Doppler velocities for ventricular inflow, or abnormal early transmitral left ventricular filling velocity, identified a group of children and adolescents at high risk for poor outcome [124].

The 2005 Bethesda Conference recommendations on competitive athletics in children and adults with cardiovascular disease recommend limitation from all competitive sports in individuals with a probable or unequivocal clinical diagnosis of HCM, regardless of age or prior treatment [125]. In genotype positive-phenotype negative individuals, regular exercise stress testing is recommended. If blood pressure response and exercise tolerance remain normal and there are no exercise-related ventricular arrhythmias, no restriction from competitive athletics is recommended [125]. The 2011 ACCF/AHA guideline allows participation in low-intensity competitive sports like golf or bowling and recreational participation in activities with low and moderate levels of exercise, with an emphasis on aerobic exercise [112].

Exercise as Nonpharmacologic Treatment of Essential Hypertension

When primary hypertension begins in childhood, a nonpharmacologic approach to lowering BP is preferable when possible, since initiation of drug treatment has known significant side effects. In other parts of this textbook, the BP-lowering effects of weight loss and diet change are presented. Here, the BP-lowering effect of exercise is reviewed.

An immediate decrease in BP occurs after exercise in all age groups and this decrease is sustained [126]. Blood pressure remains lower for the rest of a 24 h period after each 30 min period of moderate exercise through a combination of decreased sympathetic activity and increased endothelium-dependent vasodilation [127]. Many epidemiologic studies in children and adolescents have shown a strong relationship between higher levels of regular physical activity and lower blood pressure. The DISC study was a randomized clinical trial of a reduced saturated fat and cholesterol diet in 8–10-year-old children with moderate baseline cholesterol elevation. Over a 3-year period, self-reported levels of physical activity were significantly correlated with blood pressure: for every 100 estimated-metabolic-equivalent hours of physical activity, systolic BP was 1.15 mmHg lower [128]. In the Muscatine study, a subset of the cohort underwent assessment of physical fitness. Increased fitness and strength correlated inversely with BP over a 5-year interval [129]. From the NHANES survey of 1998–2002, a subset of 3,110 adolescents and 2,205 adults underwent maximal treadmill exercise testing. Cardiorespiratory fitness was estimated by exercise duration with 33.6 % of adolescents and 13.9 % of adults classified as having low fitness. Systolic blood pressures were significantly higher in the low versus high fitness groups [130]. In another analysis of these NHANES adolescent results, higher systolic BP clustered with adiposity, insulin resistance, and dyslipidemia in the lowest quintile of cardiorespiratory fitness [131]. In the Northern Ireland Young Hearts project, a random cohort of 12–15-year-old adolescents underwent cardiovascular risk assessment. Over a 3-year interval, there was a significant relationship between increased self-reported physical activity and lower blood pressure [132]. In the Young-HUNT study from Norway, activity levels, weight measures, and BP were evaluated in more than 8,000 adolescents. In this population, low levels of

physical activity were significantly associated with higher mean diastolic BP and increased odds of overweight and obesity [133].

The effects of specific activity interventions on blood pressure in children and adolescents have been evaluated in a series of randomized controlled trials. These have been systematically reviewed in a recent meta-analysis [134]. The review included 12 trials representing 16 outcomes in 1,266 subjects. Sample size ranged from 16 to over 500 subjects and age ranged from 7 to 19 years. The training period varied from 8 to 36 weeks with frequency ranging from two to five times a week and duration from 10 to 75 min per session. Ten trials used primarily aerobic training and two used resistance training. Collectively, the studies showed a 1 % reduction in systolic BP and a 3 % reduction in diastolic BP. Subsequent trials confirm significant blood pressure-lowering effects of exercise interventions in children [135–137]. In one of these trials in obese prepubescent children, late follow-up after 2 years showed significantly lower BP on ambulatory monitoring correlated with higher levels of physical activity and lower BMI [138]. Although the magnitude of change in blood pressure in these studies is not large, it occurs at a time when blood pressure is normally increasing. Both the epidemiologic studies and the intervention trials indicate that the age-related rise in blood pressure may be blunted by frequent, regular activity. Combining this with knowledge of the strong association between hypertension and obesity and the established benefits of exercise in weight control, regular dynamic physical activity should be a standard part of the management of primary hypertension in children and adolescents.

Exercise Recommendations in Hypertensive Athletes

Activity recommendations for specific BP-related subgroups of children have been included throughout this chapter. As noted in the section describing the exercise response in hypertensive children and adolescents, the 2005 Bethesda Conference recommendations on competitive exercise in individuals with cardiovascular disease address systemic hypertension without distinguishing children and adolescents from adults [36]. The BP-lowering effects of repetitive exercise are reviewed and regular dynamic activity is recommended. Intensive resistive training is not recommended. Participation in competitive athletics is limited only "until BP is controlled by appropriate treatment." The American Academy of Pediatrics Council on Sports Medicine and Fitness released new recommendations for athletic participation by children and adolescents with systemic hypertension in 2010 [37]. Daily physical activity is recommended regardless of BP status. Individuals with prehypertension or grade one hypertension are not limited from participation in competitive athletics. Youth with stage two hypertension are restricted from high-static sports until BP is in the normal range. These guidelines and many other expert commentaries have recommended regular dynamic exercise and no exercise limitation in hypertensive children and adolescents on effective therapy [30, 38–40].

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Non-pharmacologic Treatment of Pediatric Hypertension

35

Sarah C. Couch and Stephen R. Daniels

Abstract

The initial approach to management of primary mild to moderate hypertension in children and adolescents is implementation of changes in lifestyle. Lifestyle intervention may also be quite important as an adjunct to pharmacologic treatment in both primary and secondary forms of hypertension. In that setting, appropriate changes in diet, physical activity, and weight management may allow the use of a lower dose of pharmacologic treatment.

It should not be surprising that lifestyle change is an important therapeutic approach because it is well recognized that hypertension results from a variety of causes, including genetics, obesity, and other environmental and dietary factors. Thus, intervening with changes in diet, increased physical activity, and weight management can disrupt those causal pathways.

In this chapter, we will explore the various non-pharmacologic approaches that have been shown to be effective in blood pressure reduction in children and adolescents. We will focus on dietary interventions, physical activity interventions, weight management, which is quite important for children and adolescents who are overweight or obese, and other interventions, such as stress reduction.

Keywords

Hypertension • Epidemiology • Hyperlipidemia • Pediatrics • Atherosclerosis • Obesity

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Diet

Many dietary factors have been studied relative to blood pressure in youth, sodium probably the most. Of the more than 20 observational studies that have been done on sodium reduction and blood pressure in children, most studies suggest a significant positive relationship [1–3]. The association between sodium and blood pressure may be more pronounced in certain groups of youth, such as African Americans, those with diabetes, and those with a family history of hypertension [4]. Blood pressure in children who are overweight or obese may also be more responsive to sodium, according to recent findings from the National Health and Nutrition Examination Survey (NHANES) 2003–2008 [5]. In this study, usual dietary sodium intake and risk for high blood pressure were compared among children and adolescents aged 8–18 years by weight status. This study found that, for those who were overweight or obese, the risk of having high blood pressure increased by 74 % for every 1,000 mg (approximately one half teaspoon of salt) per day increase in sodium intake, whereas the risk increased only 6 % in non-overweight children and teens. Mechanistically, blood pressure of obese adolescents may be particularly sensitive to changes in sodium intake due to the higher activity of the sympathetic nervous system and hyperinsulinemia [6, 7]. Both conditions have been shown to alter urinary sodium excretion in children, adolescents, and young adults [8, 9].

Salt is the major source of sodium in children's diets, and 80 % of the salt children eat comes from processed foods and restaurant fare [10]. When salt intake is reduced in the diets of infants and children, on average, blood pressure responds favorably. As evidence, a meta-analysis from 13 randomized controlled salt reduction trials showed that even a modest decrease in salt intake in the diets of youth was associated with a small but significant decrease in blood pressure [11]. Current sodium intakes among children in the USA are well above adequate intake (AI) levels [12]. Given this, the National High Blood Pressure Education Program (NHBPEP) suggests that all children may benefit from lowering dietary sodium from the current intakes to AI levels, which are 1.2 g/day for 4–8 year olds and 1.5 g/day for older children [13].

For infants, breast milk on average has lower sodium content along with many other nutritional benefits [14]. Exclusive breast-feeding has been associated with early cardiovascular benefits including lower blood pressure [15], lower cholesterol levels, and lower body mass index compared to formula-fed infants [16, 17]. The Surgeon General's Office, the World Health Organization, the American Academy of Pediatrics, and the American Academy of Family Physicians recommend exclusive breast-feeding through the first 6 months of life for this and other reasons.

Supplementation trials with calcium and potassium either alone or in combination have resulted in significant blood pressure lowering in adults, but studies in children have been too few to draw definitive conclusions. In three calcium supplementation trials [18–20], doses ranged from 600 to 1,000 mg/day, trial duration ranged from 4 to 12 weeks, and blood pressure lowering was variable with lower systolic blood pressure reported in two studies [18, 19] and lower diastolic blood pressure in the third [20]. On average, blood pressure reductions were greater in those with hypertension and low calcium intakes pretreatment (<800 mg/day). Potassium supplementation trials have been equally variable in dose and duration; longer-term trials with doses of 1,500 mg/day resulted in lower age-related blood pressure increases in systolic and diastolic blood pressure compared to non-supplemented children [21]. Both calcium and potassium supplementation have been shown to induce urinary sodium excretion [21, 22]; this likely contributes to the hypotensive effects observed. At present, there is too limited data on these minerals to support clinical recommendations for use in blood pressure management in children.

Other nutrients that have been associated with blood pressure levels in children include magnesium [23, 24], folic acid [25, 26], unsaturated fat [27–29], dietary fiber [27, 30], and total fat [28, 29]; however, these associations have been small

and findings inconsistent. Many of these associations have been derived from cross-sectional data, where independent associations are often difficult to ascertain because of the intercorrelation of multiple nutrients in the diet. Also, nutrient-based approaches fail to take into account the potential synergistic effects between nutrients, other food components, and blood pressure. Recent research on dietary patterns considers these factors and offers promising information on the effects of the diet as a whole on blood pressure and other cardiovascular risk factors. In adults, a dietary pattern high in fruits and vegetables (8–9 servings/day), low-fat dairy products (2 servings/day), and low in red meat and refined carbohydrates was shown to lower systolic and diastolic blood pressure within 2 weeks of initiation, independent of body weight changes [31]. The effects of this diet, which is also known as the Dietary Approaches to Stop Hypertension (DASH) diet, were more significant for those with hypertension and were enhanced by sodium reduction [32]; also see www.dashdiet.org.

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 (≥4 servings/day) plus dairy products (≥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 body mass index [33]. Couch et al. [34] 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 diet high in fruits and vegetables and low-fat dairy foods and that was low in fat and sodium as well as high in potassium. More recently, Damasceno et al. [35] showed that regular consumption of fruits (≥2 servings per day) was associated with lower systolic and diastolic blood pressure. Greater consumption of vegetables (>2 servings/day) was associated with lower systolic blood pressure in a study of approximately 800 adolescents in Brazil. Greater adherence to a DASH-type diet was also shown to be associated with lower risk of hypertension in adolescents with diabetes [36]. Taken together, these findings suggest that a dietary pattern emphasizing fruits, vegetables, and low-fat dairy foods may be beneficial in the prevention and management of elevated blood pressure in children and adolescents. Additional studies are needed to confirm these relationships and to determine whether this dietary pattern is achievable and effective in children at risk for cardiovascular disease. 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 [13]. 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.

Physical Activity

The association of lower levels of physical activity and higher levels of blood pressure has been demonstrated in epidemiologic studies of adults and children. For example, Sallis et al. found that the level of physical activity was inversely related to diastolic blood pressure in young adults [37]. In longitudinal studies, low levels of physical activity have been shown to be associated with higher rates of development of hypertension [38]. In children, Gidding et al. showed that higher self-reported physical activity was associated with lower systolic blood pressure [39].

It is these epidemiologic relationships that have led to consideration of using increased physical activity as a therapeutic approach to elevated blood pressure. Since these relationships are not limited to individuals with hypertension, it has also been suggested that physical activity can be used as an approach to the prevention of hypertension and, more specifically, in pediatric patients with prehypertension [40].

In adults, numerous clinical trials have evaluated the effect of increasing physical activity on blood pressure. Most studies have focused on

physical activity programs utilizing aerobic exercise. Aerobic exercise is defined as exercise that is usually rhythmic, involving use of large muscle groups, which results in increased heart rate and respiratory rate. Examples of aerobic activity include walking, running, cycling, and swimming. Fewer trials have evaluated the impact of resistance exercise, such as weight training. Meta-analyses have been done on clinical trials of both aerobic [41, 42] and resistance [43] activity and their relationship to blood pressure in adults.

The studies of aerobic exercise have included individuals with normal blood pressure, prehypertension, and hypertension. The meta-analyses of aerobic exercise show that it is associated with a reduction of systolic blood pressure ranging from 2 to 7 mmHg. The largest declines in blood pressure seen with aerobic activity occur in studies of patients with hypertension.

The studies of resistance activity show a reduction of systolic blood pressure from 3 to 6 mmHg. Of interest is that increased physical activity appears to lower blood pressure in adults independent of any effect on lowering weight or body mass index.

While different regimens have been used to increase aerobic activity, the most common protocol uses 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. These results taken together have resulted in recommendations to include increased physical activity in the non-pharmacologic regimen for treating hypertension in adults [44]. 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 % V02 R) for greater than 30 min per day on most, preferably all, days of the week. They suggested that endurance physical activity should be the primary form but that this could be supplemented by resistance activity [44].

The mechanisms by which physical activity reduces blood pressure are not completely understood [45]. Possible mechanisms include changes in neurohumoral, vascular, and cardiac structural features. Catecholamine concentrations and insulin resistance decrease in response to chronic exercise; peripheral vascular resistance decreases in response to both acute and chronic endurance activity.

There have been 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 [46]. 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 [47]. For example, Danforth et al. used a walking/jogging program in a group of 12 African American children with hypertension [48]. 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 participant 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 [49]. 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 of 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 [50]. 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 has addressed these issues in a policy statement published in 2010 [51]. 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. 35.1). 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.

Weight Management

Obesity is one of the strongest determinants of blood pressure [52]. In recent years, the average blood pressure and the prevalence of hypertension in children and adolescents have gone up [53, 54]. A major part of the explanation for this rise in blood pressure is the increasing prevalence and severity of obesity in this age group [55].

Because of the strong relationship between obesity and hypertension, weight management has been a mainstay of non-pharmacologic treatment for individuals with elevated blood pressure and overweight or obesity. Studies have shown that a 10 kg weight loss in adults is associated with a 5–20 mmHg drop in systolic blood pressure [56]. However, it is important to inform patients that they do not need to reach an ideal body weight to see important improvements in blood pressure.

It is currently estimated that the prevalence of obesity in children and adolescents in the USA is about 17 %. When overweight is combined with obesity, the prevalence is approximately 32 % [55]. There are fewer studies that have evaluated the impact of improvement of body mass index on blood pressure in children and adolescents. Kirk et al. demonstrated that, in the context of a clinical weight management program, improvement in body mass index is associated with improvement in systolic blood pressure as well as other cardiovascular disease risk factors [57]. Reinehr et al. evaluated the changes in cardiovascular risk factor profile in relation to the degree of weight loss in children and found that blood pressure reduction is achieved with weight loss [58]. In pediatric studies, a reduction in BMI of 8–10 % is associated with an 8–10 mmHg reduction in blood pressure [57, 58].

The best approach to weight management for pediatric patients has been published [50, 59]. This includes a strong focus on behavior change related to improving diet and increasing the level of physical activity. This approach includes the behavior change principles of stimulus control, goal setting, recording of diet and activity (monitoring), and rewards. 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 body mass index, 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

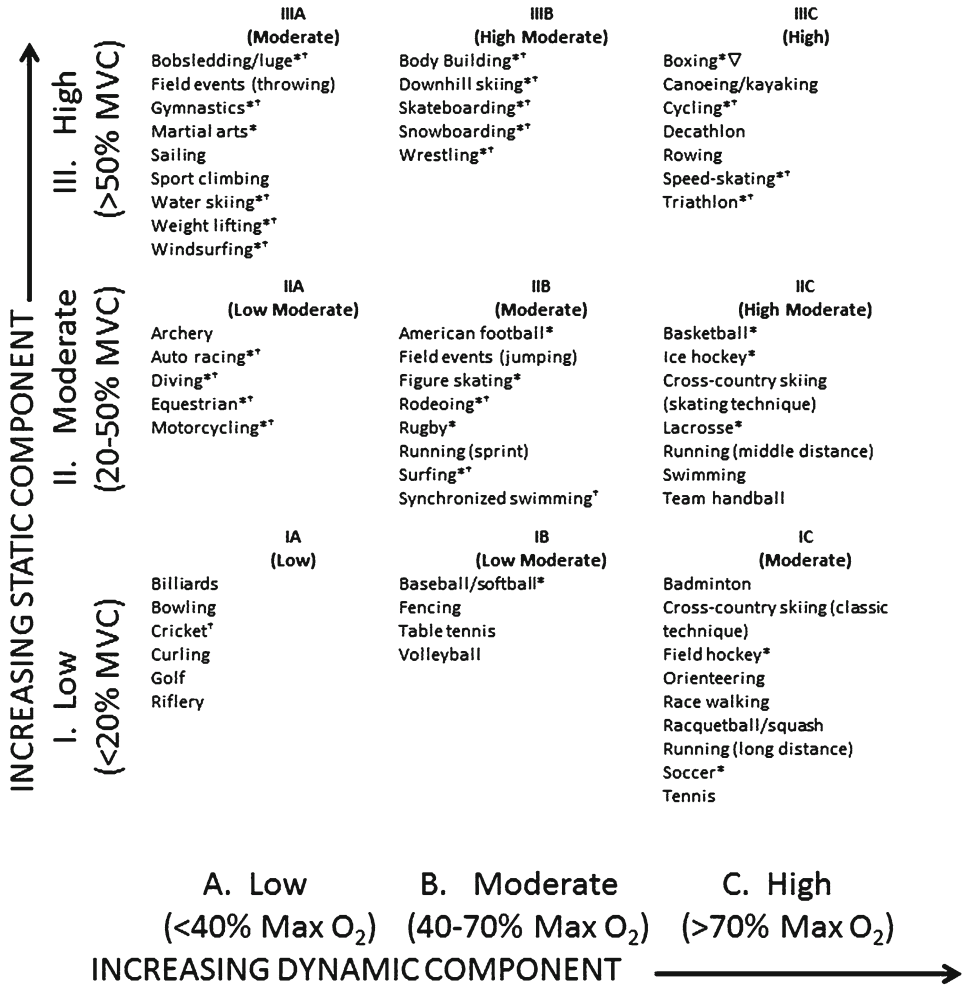

Fig. 35.1 Classification of sports according to cardiovascular demands (based on combined static and dynamic components). This classification is based on peak static and dynamic components achieved during competition. It should be noted, however, that the higher values may be reached during training. The increasing dynamic component is defined in terms of the estimated percent of maximal oxygen uptake ($Max0_2$) achieved and results in an increasing cardiac output. The increasing static component is related to the estimated percent of maximal voluntary contraction (MVC) reached and results in an increasing blood pressure load. The lowest total cardiovascular demands (cardiac output and blood pressure) are shown in *Box IA* and the highest are shown in *Box IIIC*. *Boxes IIA, IB, IIIA, IIB, IC, IIIB*, and *IIC* depict low-moderate, moderate, and high-moderate total cardiovascular demands. These categories progress diagonally across the table from lower left to upper right. *Danger of bodily collision. †Increased risk if syncope occurs. ▽Participation not recommended by the American Academy of Pediatrics. †The American Academy of Pediatrics classifies cricket in the IB box (low static, moderate dynamic) (Reprinted from Rice SG; American Academy of Pediatrics, Council on Sports Medicine and Fitness. Medical conditions affecting sports participation. *Pediatrics.* 2008;121(4):841–848; originally adapted from Mitchell JH, Haskell W, Snell P, Van Camp SP. 38th Bethesda Conference. *J Am Coll Cardiol.* 2005;45(8):1364–1367, with permission from Elsevier)

and their family understand the changes to be made and helps the clinician understand the perceived barriers to change [60]. 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.

Other Non-pharmacologic Approaches

Some other approaches to therapy, such as relaxation and stress reduction, have been proposed in the treatment of hypertension in adults. However, controlled trials of relaxation therapies have not shown a consistent and significant effect on blood pressure. In children and adolescents, a variety of stress reduction techniques, including meditation and progressive muscle relaxation, have been investigated [61, 62] with mixed results. At present, it is not recommended that relaxation and stress reduction be utilized in the standard clinical approach to children with hypertension. Nevertheless, further research in this area is warranted.

Conclusions

Non-pharmacologic treatment is quite important in the management of hypertension in children and adolescents. Several interventions, including changes in diet and physical activity, now present true evidence-based approaches to management. However, many questions remain unanswered or only partially answered. What is the optimum diet for children with hypertension? Is the answer the same for all patients or might there be some patients who respond better to some dietary changes than others? What is the best regimen of physical activity, including intensity, duration, and frequency of physical activity? 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 non-pharmacologic therapy in the future.

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Pharmacologic Treatment of Childhood Hypertension

36

Michael A. Ferguson and Joseph T. Flynn

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. As a result, care providers are increasingly expected to appropriately evaluate and treat hypertensive pediatric patients. This chapter provides an overview of antihypertensive drug therapy in children, including indications for treatment and approaches to optimizing BP control. A detailed review of available antihypertensive agents is provided with an emphasis on pediatric-specific data with respect to dosing, efficacy, and safety.

Keywords

Pharmacotherapy • Clinical trials • Diuretics • Vasodilators • Calcium channel blockers • ACE inhibitors • Angiotensin receptor blockers • Beta-adrenergic blockers

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 [1, 2]. 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 [3, 4]; 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 [5]. Although they reported a prevalence rate of only 0.8 % in 12–17-year-olds, the definition used for

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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 % [5]. 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 short-term and long-term overall 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 [6]. 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 presented in the National High Blood Pressure Education Program's (NHBPEP) Fourth Report published in 2004 [7]. Table 36.1 provides the classification schema for BP in childhood from the Fourth Task Force Report.

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 [8, 9]. 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 adolescents with hypertensive BP readings has doubled in the last two decades, with 3–5 % now affected [10–12]. In addition, there has been a concomitant rise in the prevalence of prehypertension, with 10–15 % of youths now affected [11, 12], as well as an increase in absolute systolic and diastolic BP values of 1.4 mmHg and 3.3 mmHg, respectively [13]. This upward trend in BP has generally been attributed to the ongoing childhood obesity epidemic.

Table 36.1 Classification of blood pressure in children

Blood pressure classification	Blood pressure percentiles
Normal	SBP and DBP < 90th percentile
Prehypertension	SBP or DBP 90–95th percentile or BP > 120/80 mmHg even if <90th percentile
Stage 1 hypertension	SBP or DBP ≥ 95–99th percentile + 5 mmHg
Stage 2 hypertension	SBP or DBP > 99th percentile + 5 mmHg

BP blood pressure, *DBP* diastolic blood pressure, *SBP* systolic blood pressure

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 evidence that primary care pediatricians remain uncomfortable with the evaluation and treatment of children with elevated BP [14, 15]. 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. Important legislative initiatives over the last 15 years, including the Food and Drug Administration Modernization (FDAMA) Act of 1997 and Best Pharmaceuticals for Children Act of 2002, have stimulated a marked increase in pediatric trials of antihypertensive agents. As a result, 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 [16]. 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 those receiving antihypertensive drug therapy, including effects on target-organ damage and cardiovascular morbidity, remain limited.

Table 36.2 Indications for initiation of pharmacologic therapy in hypertensive children

Clinical indication	Blood pressure goal[a]
Persistent hypertension despite therapeutic lifestyle changes	<95th percentile
Hypertension with associated end-organ damage	<90th percentile
Hypertension in the setting of chronic kidney disease	<90th percentile
Hypertension in the setting of diabetes mellitus (types 1 or 2)	<90th percentile
Secondary hypertension	<90th percentile
Symptomatic primary hypertension	<95th percentile

[a]based on casual/office blood pressure measurement

General Approach to the Hypertensive Child

The Fourth Report of the NHBPEP provided 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 were provided that include the 50th, 90th, 95th, and 99th percentiles by gender, age, and height percentiles. Based on these guidelines, annual BP screening is presently recommended in all children >3 years of age; routine BP measurement in children <3 years is limited to those with increased risk of hypertension [7].

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 [17–19], ambulatory BP monitoring (ABPM) is increasingly utilized to confirm elevated office readings (see Chap. 11). 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 (as detailed in Chaps. 29 and 32). 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 (see Chap. 35). In childhood, drug therapy for hypertension is typically reserved for patients with definite indications, as outlined in Table 36.2.

In the adult population, death from ischemic heart disease and stroke increases progressively and linearly from systolic blood and diastolic BPs of 115 mmHg and 75 mmHg, respectively [20]. 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 [21]. Cardiovascular events are rare in children and, therefore, are not practical end points in the study of antihypertensive therapies. Although subclinical end-organ damage (left ventricular hypertrophy, increased carotid artery intimal-medial thickness; discussed in detail in Chap. 29) [22–24] 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 NHBPEP Fourth Task Force Report, in uncomplicated primary hypertension, the goal should be reduction of BP to less than the 95th percentile. In the setting of concurrent disease or target end-organ damage, BP should be lowered to less than the 90th percentile [7]. Recent recommendations by the European Society of Hypertension

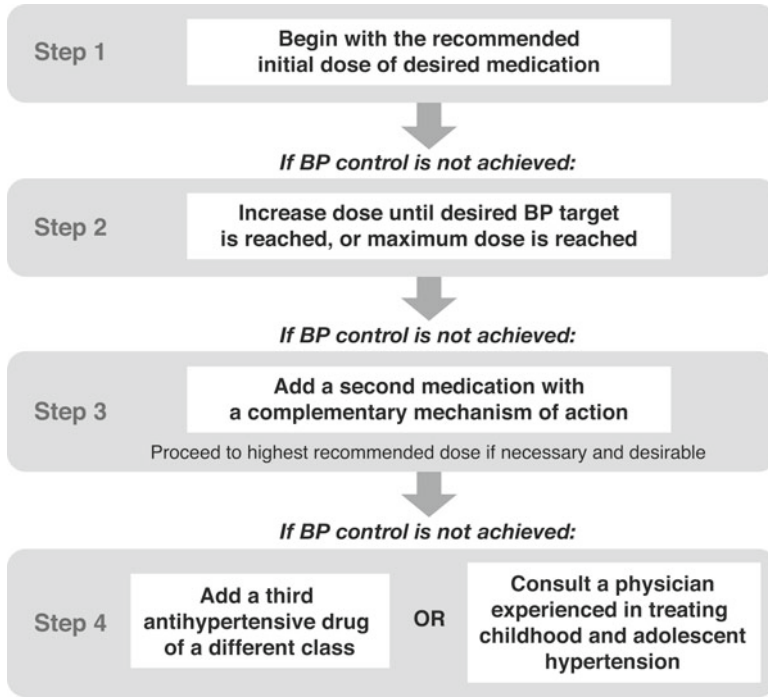

Fig. 36.1 Stepped-care approach to prescribing antihypertensive medications in children and adolescents

advocate for more rigorous BP control, with 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 [16]. These goals 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 [25]. One comment about these recommendations is that they are based on ABPM targets; how they relate to the usual approach to treatment using office BP values remains unclear at this time.

When antihypertensive drug therapy is necessary, a stepped-care approach (see Fig. 36.1) to the initiation and escalation of drug dosing is typically recommended [7, 26]. After a first-line agent is selected, it should be started at the lowest recommended dose range 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 or replacement of the first agent altogether.

Given the lack of pediatric data on the optimal first-line agent, selection of an initial antihypertensive agent is largely dependent on the judgment of the individual provider. Although specific drugs may be preferential in particular clinical settings based on putative benefits or predicted response (see below, Directed Therapy), considerable variation exists in the choice of a first agent, particularly in the setting of primary hypertension. A survey of pediatric nephrologists revealed that 47 % used angiotensin-converting enzyme (ACE) inhibitors, 37 % calcium channel blockers (CCBs), 15.3 % diuretics, and 6.6 % beta-adrenergic blockers as first-line therapies in primary hypertension [27]. Studies comparing the efficacy of the different classes of antihypertensive medications in children are lacking. The vast majority of 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 [28], with ACE inhibitors, angiotensin II receptor antagonists (ARBs), and CCBs demonstrating similar antihypertensive efficacy [29]. In addition to assessing putative benefit and likelihood of response to a particular agent, it is also important to consider potential adverse effects prior to initiating therapy. For example, noncardioselective beta-adrenergic blockers are generally avoided in those with reactive airway disease due to an increased risk of bronchospasm [30] and ACE inhibitors/ARBs are absolutely contraindicated in pregnancy due to the potential for fetopathy [31].

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 36.3 provides dosing guidelines for medications commonly used in hypertensive children.

Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors have a number of modulatory effects on the renin-angiotensin-aldosterone system (RAAS) 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 [32].

Relative to other antihypertensive classes, ACE inhibitors have the largest body of evidence supporting their use in pediatric patients [33]. The large majority of these agents have been systematically studied in FDAMA-related industry-sponsored trials. As a result, there are robust pediatric specific data related to dosing, efficacy, and safety.

Captopril, the first orally available ACE inhibitor, was developed in 1975 and received FDA approval for the treatment of adult hypertension in 1981 [34, 35] In 1979, Oberfield et al. [36] 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 [37–41]. 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 [7] 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. Disadvantages of captopril include it's short duration of action, necessitating three times daily dosing.

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) [42, 43]. Minimum effective doses were similar for enalapril and lisinopril (0.08 mg/kg/day 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. As a result of these trials, FDA-approved labeling for enalapril and lisinopril includes clear dosing guidelines as well as instructions for preparation of an extemporaneous suspension [44].

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 [45].

Table 36.3 Medications for the treatment of hypertension in children

Class	Drug	Starting dose	Interval	Maximum dose[a]
ARAs	Eplerenone	25 mg/day	QD–BID	100 mg/day
	Sprinolactone[b]	1 mg/kg/day	QD–BID	3.3 mg/kg/day up to 100 mg/day
ARBs	Candesartan[b]	1–6 years: 0.2 mg/kg/day	QD	1–6 years: 0.4 mg/kg/day
		6–17 years: <50 kg 4–8 mg QD		6–17 years: <50 kg 32 mg daily
		>50 kg 8–16 mg QD		>50 kg: 32 mg daily
	Losartan[b]	0.7 mg/kg/day (up to 50 mg QD)	QD	1.4 mg/kg/day (max 100 mg QD)
	Olmesartan[b]	20–35 kg: 10 mg QD	QD	20–35 kg: 20 mg QD
		>35 kg: 20 mg QD		>35 kg: 40 mg QD
	Valsartan[b]	<6 years: 5–10 mg/day	QD	<6 years: 80 mg QD
		6–17 years: 1.3 mg/kg/day (up to 40 mg QD)		6–17 years: 2.7 mg/kg/day (up to 160 mg QD)
ACE inhibitors	Benazepril[b]	0.2 mg/kg/day (up to 10 mg/day)	QD	0.6 mg/kg/day (up to 40 mg/day)
	Captopril[b]	0.3–0.5 mg/kg/dose	BID–ID	0.6 mg/kg/day (up to 450 mg/day)
	Enalapril[b]	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[b]	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
α- and β-adrenergic antagonists	Carvedilol[b]	0.1 mg/kg/dose (up to 6.25 mg BID)	BID	0.5 mg/kg/dose up to 25 mg BID
	Labetalol[b]	2–3 mg/kg/day	BID	10–12 mg/kg/day (up to 1.2 g/day)
β-adrenergic antagonists	Atenolol[b]	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[c]	1 mg/kg/day	BID–QD	8 mg/kg/day (up to 640 mg/day)
CCBs	Amlodipine[b]	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
	Isradipine[b]	0.05–0.15 mg/kg/dose	TID–QD	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)
Central a-agonist	Clonidine[b]	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[c]	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–QD	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)

ACE angiotensin-converting enzyme, *ARA* aldosterone receptor antagonist, *ARB* angiotensin II receptor blocker, *CCB* calcium channel blocker, *HCTZ* hydrochlorothiazide

[a]The maximum recommended adult dose should not be exceeded

[b]Information on preparation of a stable extemporaneous suspension is available for these agents

[c]Available as a FDA-approved commercially supplied oral solution

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 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 [44]. Of note, post hoc analysis of the fosinopril trial results demonstrated reduced efficacy in black children compared to non-black children, a finding similar to studies of ACE inhibitors in adults [46, 47].

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 [48]. Dose-response analysis demonstrated positive slopes for both systolic and diastolic BP, though it did not reach statistical significance [48]. 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 [48]. The authors speculated that this was related to the trial design and the extremely long-acting effects of ramipril compared to other ACE inhibitors (R Portman, personal communication). 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.

Angiotensin Receptor Blockers

ARBs, like ACE inhibitors, produce a BP-lowering effect through modulation of the RAAS. Specifically, ARBs act by inhibiting the activation of the AT_1 receptor by angiotensin II [49]. Therefore, the actions of angiotensin II on the AT_1 receptor, as described previously, are downregulated by ARBs, leading to increased effects on the AT_2 receptor. ARBs do not, however, affect the bradykinin system.

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 [44], 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 [50]. After 3 weeks of therapy, significant dose-dependent reductions of diastolic and systolic BP were demonstrated. During the randomized placebo washout 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 trial of losartan in hypertensive children aged 6 months to 6 years is ongoing, but no longer recruiting participants [51].

Candesartan has been studied in pediatric patients ranging in age from 1 to 17 years [52, 53]. 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 [52]. 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 non-blacks. Response appeared to be sustained over a 52-week open-label 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 [53]. 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 pre-planned 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 [53]. FDA-approved labeling includes dosing recommendations for children 1–17 years as well as instructions for the preparation of a stable oral solution [44].

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 [42]. 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 only two serious adverse events that were thought to be drug related. 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 [54].

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 [55]. This study included a separate cohort of black children. Although BP-lowering efficacy was observed in patients of all ethnic backgrounds, the predominantly non-black 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 [56, 57]. However, a later study did not find a significant effect on systolic BP at doses ranging from 0.5 to 4.5 mg/kg [38].

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 as well.

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 [58]. This knowledge, in combination with emerging adult

data showing a decrease in mortality in patients with severe heart failure treated with aldosterone blockade [59, 60], 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. A recent observational study reported acceptable safety and tolerability profiles in children receiving spironolactone, largely as part of multidrug diuretic regimens in the setting of heart disease or chronic lung disease [61]. No BP data were reported and adverse events were limited to dyskalemia. Problematic progesterone-like and antiandrogenic adverse effects can be seen in adults due to nonspecific binding to steroid receptors, including gynecomastia, erectile dysfunction, and decreased libido in men and menstrual abnormalities in women [62, 63]. Although instructions for preparation of an extemporaneous suspension are available for spironolactone, only unlabeled pre-FDAMA dosing guidelines exist for the treatment of hypertensive children.

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 [64]. Reductions in both systolic and diastolic BP were achieved on therapy; however, this reached significance only in the high-dose group. No dose-response effect was demonstrated. There were few adverse events reported during the trial, though the brief duration of the study precluded assessment of tolerability with chronic use.

Beta-Adrenergic Antagonists

The β-adrenergic antagonists are a large class of medications with heterogeneous pharmacologic properties. They act by blocking stimulation of β1- and β2-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 [65]. All currently available agents antagonize cardiac β1-receptors competitively, but vary in the degree of β2-receptor blockade in extra cardiac tissues. In addition, there are other β-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 [66].

Most β-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 evidence-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 [67]. 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 [68]. However, there was a 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 β-adrenergic antagonist available in the United States and, historically, is the most extensively used in children and adolescents [69]. 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, though these involve a limited number of subjects making it difficult to draw conclusions with respect to efficacy and safety [70–72]. It should be noted that propranolol is available in a commercially available oral solution.

Vasodilatory β-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 α1-receptor blockade and nebivolol induces endothelium-dependent vasodilation by stimulating nitric oxide activity [73]. Whereas conventional β-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 have been specifically studied for hypertension in the pediatric population.

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 [69].

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.

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 [74–77]. 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 [78]. Pediatric data suggest that short-acting nifedipine may be used safely with judicious dosing in otherwise healthy children [79, 80]; however, many recommend abandoning its use in children given the availability of safer alternatives [81, 82]. 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 [83]. 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 [84]. 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 [85–87]. 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 the use of isradipine 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 [88]. 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. A highly variable kinetic profile

similar to that seen in young adults was noted in a small number of pediatric transplant patients who underwent pharmacokinetic testing [89]. 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 [90]. In addition, compliance was significantly better in those treated with felodipine. In the industry-sponsored clinical trial, felodipine 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 or higher doses [91].

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 [92–96]. 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 [97]. 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 [98]. 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 [99]. 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 [100, 101]. Instructions for formulation of the suspension are available on the FDA-approved labeling.

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.

Direct Vasodilators

Vasodilators, such as minoxidil and hydralazine, reduce BP by relaxing arterial smooth wall 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 [102–104]. No controlled clinical trials in children have been performed and long-term safety data is lacking. Minoxidil use in children has generally been reserved for those with severe refractory hypertension due to the high incidence of hypertrichosis in those with long-term exposure. 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, so little is known about the efficacy or safety of these agents in children. Alpha-blockers play an important role in 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 [105]; however, there

is a poor side effect profile and risk for rebound hypertension when the medication is discontinued suddenly.

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. In an effort to maximize benefit, a targeted approach to therapy should be employed. Given the higher prevalence of secondary hypertension in children, the pathophysiologic mechanism of BP escalation can often be identified. In some cases, this facilitates selection of a specific therapeutic agent. In patients with concomitant diseases such as diabetes, a particular drug may be particularly beneficial. A thorough review of this topic is beyond the scope of this chapter; however, the following section provides a brief discussion of some clinical situations where a specific antihypertensive agent may be particularly advantageous. Indications for directed therapy with corresponding medications are provided in Table 36.4.

Table 36.4 Indications for specific/directed drug therapy

Condition	Drug
Renal artery stenosis	ACE-I, ARB, diuretic, vasodilator
Diabetes (type 1 or type 2)	ACE-I, ARB
Coarctation of aorta	Beta-agonist
Renal parenchymal disease	ACE-I, ARB
Liddle syndrome	Amiloride
Glucocorticoid remediable aldosteronism	GC, eplerenone, spironolactone
Gordon syndrome	Thiazide diuretic
Pheochromocytoma	Sequential alpha- and beta-agonists
Posttransplant hypertension	CCB, ACE-I, ARB

Renovascular Hypertension

In the setting of renal artery stenosis, perfusion to a part or to the entire kidney is compromised, stimulating the release of renin and subsequent upregulation of the entire RAAS [106, 107]. In this setting, angiotensin blockade with ACE inhibitors or ARBs are obviously rational choices to treat blood pressure elevation. Unfortunately, such therapy carries a risk of acute kidney injury due to relaxation of the afferent arteriole and concomitant reduction in glomerular capillary hydrostatic pressure. For this reason, bilateral renal artery stenosis is considered an absolute contraindication to ACE inhibitor or ARB treatment. However, if disease is isolated to one side or to segmental renal arteries, these medications are generally safe and particularly effective. Gradual dose titration and judicious monitoring is mandated. Given the increased renin secretion, there is always sodium retention and volume overload in patients with renovascular hypertension; therefore, diuretics and vasodilators may also play important roles in therapy.

Chronic Kidney Disease

Hypertension is common in children with chronic kidney disease. Recent analysis of data from the ongoing Chronic Kidney Disease in Children cohort revealed a prevalence rate of 54 %. [108]. Uncontrolled hypertension, hyperfiltration, and proteinuria are known risk factors for accelerated renal decline in adult patients [109–111]. There is a preponderance of evidence that angiotensin blockade slows the progression of renal decline in adults, likely secondary to antihypertensive, antiproteinuric, and antifibrotic properties [112–114]. Relative to adult studies, there is a dearth of pediatric data regarding similar benefits in children. One notable exception is the ESCAPE trial, which reported that treatment with ramipril was effective in reducing systolic and diastolic BP in a cohort of pediatric patients with CKD [25]. All subjects in this study received ramipril at the highest antihypertensive dose approved in adults (10 mg/day) adapted for

body size (6 mg/m^2/day), some on combination with other antihypertensive agents to achieve desired BP control. Final analysis of this trial showed that intensive blood pressure control, defined as 24-h mean arterial pressure <50th percentile, led to significantly fewer patients reaching the primary end point, defined as 50 % reduction in GFR or progression to ESRD. Overall, there appears to be general agreement that ACE inhibitors and ARBs should be considered as first-line therapy for hypertensive therapy in children with CKD. Given the risk for depressed GFR and hyperkalemia in this population, judicious monitoring of electrolyte balance and renal function is mandated. The management of hypertension in chronic kidney disease is discussed in detail in Chap. 22.

Primary Hypertension

Primary hypertension is an increasing problem in childhood, largely the result of the ongoing obesity epidemic [10]. Some of these patients may be managed successfully with therapeutic lifestyle interventions; however, treatment with antihypertensive medications is often required. Generally speaking, choice of an agent in this setting is based on provider preference and experience rather than pathophysiologic underpinnings. In the adult population, evidence has emerged to suggest that a renin-guided approach in these patients 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 [115, 116]. 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. Low-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, β-adrenergic antagonist). Recent data suggest that such an approach is efficacious [117, 118]. 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 [119]. There is no body of evidence that such an approach is effective in pediatric patients and further studies in this age group are warranted.

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, cardiovascular morbidity, and mortality. When medications are required, a rational approach to selecting an appropriate agent with respect to pathophysiology, potential benefit, and the likelihood for side effect is advocated.

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Management of Hypertensive Emergencies

37

Craig W. Belsha

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

BBB	Blood-brain barrier
BP	Blood pressure
ECG	Electrocardiogram
ICD	International classification of diseases
IV	Intravenous
JNC	Joint National Committee
PKC	Protein kinase C
PRES	Posterior reversible leukoencephalopathy syndrome

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 [1]. 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 [2]. The purpose of this staging system is to help distinguish mild hypertension from more severe hypertension where more immediate and extensive evaluation is indicated (Table 37.1) [1]. School-based screenings report an incidence of stage 1 hypertension in 2.6 % and stage 2 hypertension in 0.6 % in adolescent students when blood pressure was measured on three separate occasions [3]. While the width of the blood pressure range in stage 1 hypertension is 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 2 hypertension may be asymptomatic or have a range of clinical signs or symptoms [4].

The terminology used to further categorize severe hypertension as a hypertensive crisis, emergency, or urgency has not been rigorously defined in childhood. The most recent report of the Joint National Committee on Detection, Evaluation, and Treatment of Hypertension, JNC 7, considers blood pressure values above 180/120 in adults to constitute a "hypertensive crisis" [5, 6]. 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.

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 [2, 6]. 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 [6].

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 encephalopathy or nephropathy. This term, however, has been removed from National and International Blood Pressure Control guidelines and is best referred to as a hypertensive emergency [6, 7]. In the International Classification of Diseases (ICD 9) coding system, "malignant hypertension" refers to any situation with severe high arterial blood pressure and not just to elevated BP associated with encephalopathy or nephropathy [8]. This term is no longer a coding modifier in the proposed ICD 10 system. 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 [9, 10].

Table 37.1 Hypertension stages

Stage	Pediatric criteria	Adult criteria
1	SBP or DBP > 95th to 99th percentile plus 5 mmHg	140–159/90–99 mmHg
2	SBP or DBP > 99th percentile plus 5 mmHg	>160/100 mmHg

Adapted from references [1, 5]
SBP systolic blood pressure, *DBP* diastolic blood pressure

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) [11]. 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 37.2). Fortunately, long-term outcome was improved with only 4 % experiencing sustained neurologic damage [12]. Another report from 1987 on 27 children and adolescents with renovascular hypertension with mean BP at presentation of 172/114 mmHg (age 5 months to 20 years) found that 85 % had evidence of target-organ abnormalities [13]. Eighteen of 27 (66 %) had left ventricular hypertrophy by ECG, 16 of 27 (60 %) had retinal vascular lesions, and 3 of 27 (11 %) renal failure.

Table 37.2 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 %

Adapted from reference [12]
BP blood pressure

A recent study evaluating 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 %) [14]. 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 [14].

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 best studied [15, 16]. 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 [17]. In adults, autoregulation appears to be present over the mean arterial pressure range from 60 to 150 mmHg [18]. Autoregulation appears early in development and is present in later fetal and neonatal lambs and neonatal dogs and humans [19, 20]. 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 [19]. 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 [19].

In adults with uncontrolled chronic hypertension, there is a shift in the autoregulatory curve, providing constant cerebral blood flow at higher mean arterial pressures [18]. 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 [21–23], the effects of chronic hypertension on developmental differences in cerebral autoregulation during childhood and adolescence remain largely unknown [24]. 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 [25].

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 through the capillary walls of the blood-brain barrier resulting in the development of hypertensive encephalopathy [26]. This impairment in autoregulation has been demonstrated in severely hypertensive adults [27], and studies have demonstrated differential effects of antihypertensive agents on cerebral blood flow during blood pressure reduction [28]. Recent studies have demonstrated a role for the delta protein kinase C (δ (delta) PKC) signaling pathway on alterations in endothelial cell tight junctions in the blood-brain barrier (BBB) in hypertensive encephalopathy [29, 30]. Inhibition of δ (delta) PKC led to the stability of the BBB in a hypertensive rat model, suggesting this may be a therapeutic target for the prevention of BBB disruption in this condition.

The mechanisms of hypertension leading to the development of hypertensive emergencies often involve the renin-angiotensin-aldosterone system [10, 31–33]. These have been reviewed in detail elsewhere [34]. High renin and aldosterone are often found in renovascular and other renal causes of hypertension. Activation of this system leads to vasoconstriction via angiotensin II production and sodium retention through the effects of aldosterone on the kidneys. Angiotensin II may also promote endothelial dysfunction and increased expression of proinflammatory cytokines such as NF-κB (kappa). Other mechanisms leading to severe blood pressure elevation may include fluid overload, as may occur in acute kidney injury or chronic kidney disease; activation of the sympathetic nervous system by secretion of vasoactive substances as in a pheochromocytoma; vasculitis; and medications [35].

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 [36–40]. Older case series have reported renal problems as the cause of hypertensive emergencies or urgencies in children in over 80 % of patients [12]. A more recent series of children treated with an intravenous antihypertensive agent reported that 55 % had associated renal disease [41]. With the increasing presence of primary hypertension in adolescence, this may become a more frequent etiology of severe hypertension in the future.

The etiologies of severe hypertension in children may vary with age and parallel the

underlying causes of hypertension in each age group [42]. 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, reflux nephropathy, 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 %) [43], 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 [44, 45]. Abrupt withdrawal of either a beta-blocker or clonidine may result in "rebound" hypertension that may require urgent intervention [46].

Clinical Presentation

Children with severe hypertension may present with major symptoms or be asymptomatic [4]. After confirming that blood pressure has been measured with the proper size of cuff and technique, the initial history and physical exam should focus on symptoms and signs of end-organ damage [47, 48]. 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 [49, 50]. Facial nerve palsy has also been observed in children with a hypertensive emergency [51–54]. Hemorrhages or exudates and papilledema are frequently reported on fundoscopic exam [55–57]. 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 [58, 59]. Skin lesions such as café au lait spots and axillary freckling may suggest neurofibromatosis, which may be associated with renovascular hypertension or pheochromocytoma [60]. Diminished femoral pulses or reduced blood pressure in the legs suggests coarctation of the aorta [47]. 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 [31, 61].

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 [62]. Adolescent girls should have a pregnancy test as preeclampsia may present with severely elevated blood pressure [63]. 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 [64, 65]. 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 leukoencephalopathy syndrome (PRES) [66–72]. If renovascular hypertension is suspected, other imaging modalities such as computed tomography angiography, magnetic resonance angiography, or direct renal angiography may be considered after blood pressure is stabilized [65, 73–75].

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 [76]. 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 [31].

A number of antihypertensive medications are available with established efficacy [75, 77, 78]. Unfortunately, few have undergone rigorous testing in children and less than half of current IV antihypertensive agents marketed in the USA have pediatric labeling [10]. 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 [79, 80]. 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 [1, 2, 5]. 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 57 children of intravenous bolus injection of diazoxide and/or hydralazine. Twenty-three percent of patients treated with bolus therapy versus 4 % of those treated with infusions experienced complications. All seven children with permanent neurologic injury were treated with bolus therapy [12].

The goal for chronic antihypertensive treatment in children is to reduce blood pressure to <95th percentile, unless concurrent conditions such as cardiac or renal disease or diabetes are present when BP should be lowered to <90th percentile [1] or to below the 75th percentile in children with chronic kidney disease without proteinuria and below the 50th percentile in cases of proteinuria [2]. 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

Table 37.3 Antihypertensive drugs for treatment of severe hypertension

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[a]	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, 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[b]	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, 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

Adapted from reference [1]
IV indicated intravenous, *IM* intramuscular, *po* oral, *ACE* angiotensin-converting enzyme, *HTN* hypertension
[a]May be used in initial treatment of hypertensive emergency at 0.1 mg/kg dose
[b]Limited reported pediatric experience; smaller doses may be needed in younger children

Treatment of High Blood Pressure in Children and Adolescents recommends lowering blood pressure by ≤25 % in the first 8 h after presentation and then gradually normalizing the blood pressure over 26–48 h to prevent complications of treatment [1]. Recently published guidelines from the European Society of Hypertension suggest that BP should be lowered by no more than 25–30 % over the first 6–8 h, followed by a further gradual reduction over the next 24–48 h [2]. 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 37.3.

Diazoxide, an intravenous direct vasodilator used frequently in the past by bolus injection [81–83], is no longer recommended as a first-line

antihypertensive agent for hypertensive emergencies [1] due to a long half-life and unpredictable duration of action [84, 85]. Use of short-acting nifedipine has been abandoned in adults [86] due to significant adverse events but continues to be used by some pediatric centers. While single and multicenter retrospective reviews have suggested this medication is safe and effective in children with in-hospital use [87–89], 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 [84, 90–94]. Short-acting nifedipine is not included in the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents for the treatment of hypertension [1] but is listed in Pediatric BP Guidelines from the European Society of Hypertension [2].

Sodium nitroprusside, a direct vasodilator of arteriolar and venous smooth muscle cells, has been used for the treatment of severe hypertension in childhood since the 1970s [95, 96]. The recommended dosage by continuous infusion is 0.53–10 μg/kg/min [1]. Nitroprusside acts by releasing nitric oxide, which dilates arterioles and venules and reduces total peripheral resistance. This decreases preload and afterload, allowing the 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 [97]. Toxicity occurs as a result of the metabolism of nitroprusside to cyanide and thiocyanate. Toxic accumulation of cyanide leads to the 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 [98]. Thiocyanate toxicity is suggested by symptoms of altered mental status, nausea, seizures, skin rash, psychosis, anorexia, or coma [85, 98]. The nitroprusside infusion should be discontinued if signs and symptoms of cyanide or thiocyanate toxicity are present. Thiosulfate administration may facilitate the conversion of cyanide to thiocyanate by donating a sulfur group [85], which may lessen the risk of toxicity. Hydroxocobalamin is an agent approved for cyanide toxicity. Most authorities recommend limiting nitroprusside use to situations where no other suitable agent is available or to brief periods of time [7, 10].

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 [99]. 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 [99]. 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 [77, 99]. 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 [100, 101]. As compared with sodium nitroprusside, systemic and cerebral vascular resistance is decreased proportionally, maintaining cerebral blood flow to a greater extent with labetalol [28]. Case series in children have demonstrated its usefulness in the pediatric population [12, 102, 103]. 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 [1, 7].

A recent retrospective single-center review of 27 infants and children (age < 24 months) treated for hypertensive crisis or stage 2 compared the response to intravenous (IV) infusions of labetalol, nicardipine, or nitroprusside [103]. 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 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 [103]. Labetalol is, however, a recommended treatment in adult patients with ischemic stroke and severe hypertension [104].

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 [105]. 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 [80]. Modest tachycardia may be seen with the 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 [100, 101] or ischemic stroke [104].

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 [106–112]. It has proven to be safe and is generally well tolerated. The recommended pediatric dosage is 1–3 μg/kg per minute [1]. 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 [113]. Phlebitis has been reported at the site of administration with higher dosage concentrations [109], 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 [114].

Hydralazine is a direct vasodilator of arteriolar smooth muscle. The mechanism of action is unclear, although it may involve alterations in intracellular calcium metabolism [77, 115]. 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 [85]. Average maximum decrease in blood pressure occurs 10–80 min after intravenous administration [31]. 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 [1]. 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. An intravenous dosage of 0.1 mg/kg could be used as an initial step for blood pressure reduction in an emergency situation until a medication such as labetalol or nicardipine has been prepared by the hospital pharmacy.

Esmolol is an ultra short-acting cardioselective β (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 [115, 116]. A trial in children with coarctation of the aorta included 116 patients less than age 6 years who received

esmolol at low (125 μg/kg), medium (250 μg/kg), or high dose (500 μg/kg). Systolic blood pressure decreased significantly from baseline on averaged 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 [115]. Pediatric studies with this agent in noncardiac conditions have not been reported.

Fenoldopam is a dopamine D_1 receptor agonist that does not act at D_2 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 [7, 117]. It has also been used as a renal protective drug in critically ill adult and pediatric patients [117, 118]. 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 μg/kg/min) [119]. Dosages of 0.8 and 3.2 μg/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 μg/kg/min) than as labeled for adults (0.05–0.3 μg/kg/min). Only a single case report of the use of this agent for a hypertensive emergency in childhood has been reported [120].

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 [7]. One pediatric case series in 10 premature neonates receiving doses of 7.4–22.9 μg/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 [121]. 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 [122]. 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 [123]. Limited experience has been reported for perioperative management of hypertension in children with this agent [124–126].

Clonidine is a centrally acting α (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 [46]. 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 [127]. 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 [128, 129], suggested dosages for severe hypertension in children have been given [1].

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 [130]. Onset of action is by 1 h with peak effect at 2–3 h when administered orally [131]. Medication half-life is 3–8 h. A stable extemporaneous suspension of isradipine may be compounded for use in small children [132]. Several pediatric series of the use of this medication for the management of hypertension have been reported [133–136]. Isradipine given sublingually to 27 adults with severe hypertension demonstrated a reduction of mean arterial pressure of 22 % by 2 h [137]. 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 drop in mean arterial pressure >25 %. The most common adverse effects included vomiting, nausea, and headache [136].

Minoxidil, an oral antihypertensive, is metabolized to minoxidil sulfate, which opens K^+ channels in vascular smooth muscle cells permitting K^+ 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 [97] often requiring concomitant use of a diuretic and β (beta)-blocking agent. Reported use in childhood includes severe chronic hypertension refractory to other medications and for acute BP elevations in children with chronic hypertension [138, 139].

Conclusion

Severe, symptomatic hypertension requires immediate evaluation and rapid institution of antihypertensive 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.

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Changes in Pediatric Food and Drug Administration Written Requests and Regulations: Impact on Clinical Trial of Hypertension Trials in Children

38

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Abstract

Regulatory changes in the United States and Europe have stimulated major pediatric clinical trials of >15 different antihypertensive agents over the last decade. With increased pediatric hypertension trial experience, trial designs have been refined and we now have a better understanding of 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 US 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.

Keywords

Pediatric hypertension • Clinical trials • Written request • Pediatric exclusivity • Trial design

Introduction

Historically, clinical trials have been neglected in the pediatric population, and consequently, the US Food and Drug Administration (FDA) has not labeled most drugs for use in children. Responding to these concerns, the US congress passed the Food and Drug Administration Modernization Act (FDAMA) in 1997 – providing for an additional 6-month period of marketing exclusivity to a drug company that responded to an FDA-issued written request for studies of their drug in pediatric patients [1, 2]. The program was expanded in January 2002 when the US congress passed the Best Pharmaceuticals for Children Act (BPCA) and again in 2003 with passage of the Pediatric Research Equity Act. It was subsequently renewed in 2007 then reauthorized without sunset in 2012, becoming a permanent part of the

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Food, Drug, and Cosmetic Act and giving children a permanent seat at the drug development table. This program has been very successful in stimulating drug studies in children, and, as a result of the program, >400 drug-labeling changes have been enacted for children [2–4]. Highlighting the importance of these studies, approximately half of the products studied have been found to have substantive differences in dosing, safety, or efficacy in children when compared with adult populations [5].

In 2006, the European Parliament followed the US example, passing legislation requiring pediatric-specific study of drugs. Both the FDA and European Medicines Agency (EMA) have developed templates that are issued by the respective agencies before initiation of pediatric exclusivity studies and contain elements of the requested studies felt to be necessary for a drug to provide a meaningful benefit to the pediatric population [2, 6]. These so-called written requests (FDA) and pediatric investigation plans (EMA) are a valuable resource that can guide antihypertensive 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. 38.1) [7]. 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 methodological issues unique to pediatric research, in addition to compliance with the formal guidelines.

Trial Design A: In trial design A, patients are randomized to placebo or one of the few different dosages of the test medication (Fig. 38.1). 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 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 [8, 9]. We have recently 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

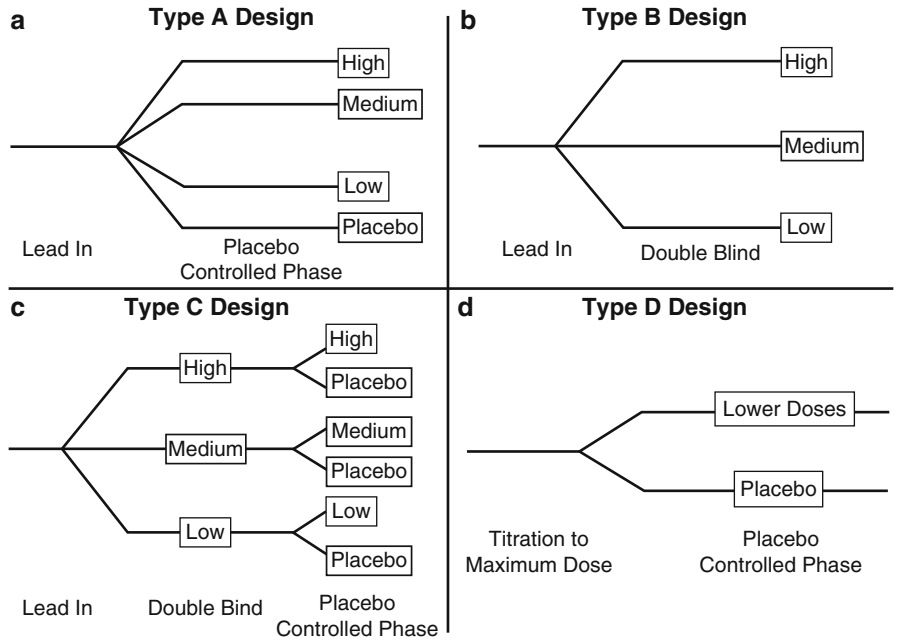

Fig. 38.1 Pediatric antihypertensive clinical trial designs

drug. Short-term exposure to placebo in pediatric trials of antihypertensive medications thus appears to be safe [10].

Trial Design B: To avoid the issues associated with a placebo-controlled trial, trial design B involves randomization to one of the two or three dosages of the test medication as in trial design A but without a placebo arm (Fig. 38.1). 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 importantly, 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.

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. 38.1). Trial C begins like trial B with randomization to one of the 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. 38.1). 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.

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 effect 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 the following:

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 ≥200 subjects ages 6–16 years and ≥50 subjects ages 1–5 years.
   (b) Trials are expected to include a mixture of black and nonblack 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 ≥95 %ile for age/gender/height or ≥90 %ile if concurrent conditions are present, based on "The Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents"[11].
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 have 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 change 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 change 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, Cmax, and Tmax 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 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 Clinical Trials.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 [12]. Table 38.1 lists the various studies completed to date. The results of many, but not all, of the clinical trials of antihypertensive agents in children have resulted in publications in scientific journals [13–32]. 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 [4]. 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 [12, 33]. 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 [14]. 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 (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 and irbesartan trials (which also failed), dosing ranges were also small, at six and nine-fold, respectively. The enalapril, lisinopril, and losartan 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.

Table 38.1 Pediatric antihypertensive drug trials completed in response to an FDA 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 age1–5/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	No age 1–5/yes age 6–16	Yes
Olmesartan	C	302	Yes	Yes

None of the failed trials investigated dose ranges higher than the corresponding adult doses. For example, the highest irbesartan dosage was 4.5 mg/kg, whereas adult data indicate that most adults need dosages up to 150–300 mg (~2–4 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 ≥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.

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 [15].

The fosinopril trial also failed to demonstrate a dose response, although it incorporated individual subject weight into the dosing [16]. 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 [34]. 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 [$p=0.001$] vs. 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 [$p=0.001$] vs. coefficient 0.08; $p=0.09$).

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 [34, 35]. 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 [16–20], while others used auscultation [13, 21, 23–27, 31, 32]. The two methods do not always agree and significant differences have been detected in certain patient populations [36, 37]. 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 [11]. 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.

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 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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