Neonatal and Infant Hypertension

30

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Abstract

Neonatal hypertension as a clinical entity has been recognized since the 1970s, and yet we still do not have a complete understanding of the physiologic blood pressure changes occurring over the first year of life. Blood pressure changes rapidly in the newborn period during hemodynamic adaptation to the extrauterine environment, especially in preterm neonates. Measurement methods have evolved to less-invasive blood pressure monitoring, but there are still improvements needed in measurement techniques. The incidence of neonatal hypertension does not seem to be increasing despite increasing complexity of the population due to technologic advances. Risk factors or causes of hypertension can be found in most infants but treatment can be challenging. Most infant hypertension resolves over time although premature and low birth weight infants are at risk of future hypertension. This chapter will describe proper measurement of infant blood pressure, illustrate the expected changes in blood pressure during the first year of life, as well as explore evaluation, management, and follow-up of neonatal and infant hypertension.

Keywords

Neonatal blood pressure • Neonatal hypertension • Infant hypertension • Blood pressure measurement • Hypertension risk factors • Hypertension management

Abbreviations

ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin-converting enzyme
ECMO	Extracorporeal membrane oxygenation
IV	Intravenous
MAP	Mean arterial pressure
NICU	Neonatal intensive care unit
PDA	Patent ductus arteriosus
RAAS	Renin-angiotensin-aldosterone system
RVT	Renal vein thrombosis
SGA	Small for gestational age
UAC	Umbilical artery catheter
VLBW	Very low birth weight

Contents

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Introduction

The incidence of hypertension in the neonatal intensive care unit (NICU) is around 1–2%. It is much less common than is neonatal hypotension, and therefore clinicians in the NICU may be less comfortable with the proper assessment and management of elevated blood pressures. In fact, around one quarter of neonates diagnosed with hypertension in the NICU are not treated with antihypertensive medications. Fortunately, various risk factors or causes of hypertension are able to be determined in most every patient. Recent studies are suggesting that hypertension in preterm infants may be different than hypertension in term infants in etiology and response to treatment. When the hypertension is related to perinatal events, the majority of neonates and infants will have normalization of their blood pressure over the first years of life. Proper management of these infants is important as there is more and more evidence that future cardiovascular health can be affected by perinatal conditions.

Measurement of Blood Pressure

The gold standard blood pressure measurement technique in neonates is direct intra-arterial monitoring. Common sites for catheterization in neonates are the umbilical and radial arteries, which have demonstrated comparable blood pressure values in this population. Direct intra-arterial monitoring may be necessary in the most acutely ill neonates although there has been a shift to noninvasive blood pressure monitoring for the majority of the neonates within an NICU. Indirect methods for measuring blood pressure include ultrasonic Doppler and oscillometric methods. Palpation and auscultation using a sphygmomanometer are not practical within the NICU setting but may be used in older infants in a clinic setting.

Ultrasonic Doppler assessment involves inflation then deflation of a sphygmomanometer with detection of blood flow or motion of the vessel wall with a Doppler device. With experienced users, the systolic blood pressure can easily be detected, but diastolic blood pressure is often unmeasurable. The technique that has become more common within the NICU and follow-up clinics is the oscillometric method. A blood pressure cuff inflates above systolic blood pressure, and then as it deflates, the oscillometric device detects the maximum pressure oscillations within the artery determining the mean arterial pressure (MAP). The machine then uses an algorithm specific to each device to calculate systolic and diastolic blood pressure. Therefore, the MAP is the most accurate pressure reading with systolic and diastolic values less precise. When oscillometric blood pressures were compared to radial arterial blood pressures in infants and children, there was good correlation between the two methods, and the oscillometric readings were better than values determined by auscultation (Park and Menard 1987). Even in premature infants, these noninvasive blood pressures correlate well with intra-arterial monitoring (Meyer et al. 2010).

As each oscillometric monitor uses independent algorithms for determination of blood pressure values, several studies have compared multiple devices for accuracy. Dannevig et al. (2005) compared three monitors: Dinamap

Compact™, Hewlett-Packard™, and Criticare™ models. When compared to intra-arterial blood pressures, they found that the Hewlett-Packard™ model had lower values than invasive monitoring, while the Dinamap™ and Criticare™ tended to read higher and that the deviance was dependent on the size of the infant. The Hewlett-Packard™ showed lower values in the larger infants, while the Criticare™ and Dinamap™ values were too high in the smallest infants which could lead to under-recognition of hypotension. Another study comparing three oscillometric devices to intra-arterial monitoring found that all three devices overestimated mean blood pressure by 3–8 mmHg (O'Shea and Dempsey 2009). Clinicians who use the oscillometric machines should be aware of the limitations of the specific device that they choose to use in order to avoid misinterpretation of blood pressure values.

The potential for under-recognition of hypotensive events is worrisome, especially in critically ill premature neonates. Takci et al. (2012) showed good correlation of invasive and noninvasive mean blood pressures except when the MAP was less than or equal to 30 mmHg where the oscillometric device readings were too high. Lalan and Blowey (2014) found oscillometry overestimated blood pressures compared to radial intra-arterial monitoring by 4–8 mmHg. While the mean MAP was similar for oscillometric measures and umbilical artery catheter (UAC) readings, the standard deviation was high at almost 10 mmHg, and therefore the authors continue to recommend intra-arterial monitoring for sick neonates.

Other less common methods of blood pressure measurement have been used by practitioners experienced in the techniques. A recent study compared blood pressure values by oscillometry, flush method, and pulse oximetry to Doppler ultrasound and found the best correlation with flush method and pulse oximetry (Ribeiro et al. 2011). Another area of debate within some NICU settings is around the use of calf blood pressure measurements. Systolic blood pressure by calf measurements is slightly lower but similar to arm measurements until about 6 months of age when the calf pressures begin to exceed arm blood pressures (Crapanzano et al. 1996). Unfortunately, the calf blood pressure values show more variability than arm blood pressures and therefore should only be used in exceptional circumstances when arm blood pressure values are not feasible prior to 6 months of age and then not used after 6 months of age.

The state of the infant at the time the blood pressure is being measured is important and can influence the blood pressure value. Early observations of blood pressures in neonates showed that the blood pressure was lower when the neonate was in deep sleep and rose above baseline when crying, being held head up, and during feeding (Gupta and Scopes 1965). The elevation of blood pressure with feeding is up to 20 mmHg higher. This observation has been confirmed in neonates within the first days of life having blood pressures increasing significantly during feeding, and the magnitude of elevation may be influenced by the volume of fluid intake within the first few minutes of feeding (Cohen et al. 1998). In follow-up clinics of infants and young children, the non-calm state has been associated with blood pressures 17–30 mmHg higher than when the infant is calm (Duncan et al. 2008). It is therefore sometimes necessary to attempt blood pressures on several occasions or in different settings in order to achieve an accurate calm measurement.

Accurate blood pressure measurement is important in neonates and infants, especially when the blood pressure factors into clinical decision-making. Some authors suggest that the median of three oscillometric blood pressure measurements should be used (Thoesen and Cowan 1992), while others state that one blood pressure during routine vitals is adequate, in calm healthy term newborns (Sarici et al. 2000). The cuff size is critically important to accurate blood pressure measurement, and the cuff width/arm circumference ratio should be between 0.45 and 0.70 (Kimble et al. 1981). As well, attention to the MAP as the most accurate measure of blood pressure is essential as this is the parameter actually measured by oscillometric devices. While physicians in critical care medicine are used to evaluating mean pressures, most pediatric nephrologists are more comfortable with systolic and diastolic blood pressures due to the use of auscultatory methods in most older children.

Table 1 Protocol for blood pressure measurement in neonates using an oscillometric device

Prone or supine position
Use right upper arm
Cuff width/arm circumference ratio between 0.45 and 0.70
Apply cuff and leave infant undisturbed for 15 min
Take readings when infant is asleep or in quite-awake state
Three blood pressure readings at 2 min intervals
1.5 h after feed or medical intervention where possible

Adapted from Nwankwo et al. (1997)

Adapting to the use of MAP within the NICU would be more useful.

The use of a standard protocol for newborn blood pressure measurement has been suggested by Nwankwo et al. (1997) (see Table 1). They found in infants weighing less than 2,500 g, when compared to routine nursing care, standardized blood pressures were significantly lower and showed less variability. First blood pressure readings were significantly higher than third readings lending support to the need for multiple measurements. Other than waiting for one and a half hours after a feed or medical intervention to take a blood pressure, the protocol is reasonable for use within the NICU setting, especially when clinical decisions are being based on the blood pressure values.

Factors Influencing Blood Pressure

Various factors, both extrinsic (maternal) and intrinsic (infant), can influence newborn blood pressure values. Maternal blood pressure and/or hypertension have been related to higher newborn blood pressures in several studies (Gillman et al. 2004; Seliem et al. 2007). Maternal age has been positively correlated with newborn blood pressure in one study (Gillman et al. 2004) but not consistently in other studies (Sedaghat et al. 2008; Sadoh and Ibhanesebhor 2010). Maternal diabetes may be related to higher newborn blood pressure especially when birth is earlier in gestation (Kent et al. 2009b). Studies on the effect of maternal smoking on infant and childhood blood pressure have been conflicting. A birth cohort study demonstrated male infants of maternal smokers had blood pressures more than 8 mmHg higher than non-smokers, although the increase was not seen in female offspring (Geerts et al. 2007). The prenatal exposure to "secondhand smoke" seems to lead to alterations in infant circulatory control mechanisms (Cohen et al. 2010). A recent study has also correlated prenatal exposure to air pollution with newborn blood pressure (van Rossem et al. 2015). Maternal body mass index >30 and low socioeconomic status were associated with higher newborn systolic blood pressure in a Nigerian study, although birth weight was still the strongest predictor (Sadoh and Ibhanesebhor 2010). Likely, even maternal nutritional intake has an effect on infant blood pressure, with a u-shaped curve for infant blood pressure and maternal carbohydrate intake (Aaltonen et al. 2008). Maternal protein intake does not seem to have the same effect in infancy (Huh et al. 2005).

Perinatal events may also influence newborn blood pressures. Antenatal steroids given within 7 days of birth can reduce respiratory distress syndrome, but the effect on newborn blood pressure has been controversial. Some studies found higher newborn blood pressures (Seliem et al. 2007; Been et al. 2009; Vesoulis et al. 2016), while others did not (Dagle et al. 2011; LeFlore et al. 2000). A recent randomized double-blind, placebo-controlled trial showed no difference in newborn blood pressures in infants that were exposed to repeated doses of prenatal corticosteroids compared to single dose (Mildenhall et al. 2009). As antenatal steroids may have an effect on function of the infant hypothalamic-pituitary-adrenal axis, the way in which the placenta handles the steroids seems to also play a role in how steroids can influence infant blood pressure (Stark et al. 2009). Maternal hemolysis, elevated liver enzymes, and low platelets or HELLP syndrome and chorioamnionitis have been associated with lower blood pressures in neonates (Been et al. 2009; Vesoulis et al. 2016). Maternal hypertension management with labetalol may be related to neonatal hypotension, while the use of other antihypertensives or magnesium sulfate does not seem to have an effect (Heida et al. 2012). Even the mode of delivery and type of maternal anesthetic may have an impact on newborn blood pressures, with elective cesarean

section and spinal anesthesia being related to lower systolic blood pressures in newborns (Sedaghat et al. 2008; Satoh et al. 2016).

The most strongly correlated intrinsic or infant factors associated with newborn blood pressure are birth weight and gestational age. The earlier in gestation that the neonate is born, the lower the expected initial blood pressure values with essentially a linear relationship (Zubrow et al. 1995; Pejovic et al. 2007). This same relationship has been shown for birth weight and blood pressure. Being born small for gestational age (SGA) may also be associated with lower initial blood pressure values (Lurbe et al. 2007). Congenital renal, cardiac, or endocrine anomalies may influence blood pressure and are associated with a higher prevalence of neonatal hypertension. The influence of fluid volume and vasoactive regulators on neonatal blood pressure is demonstrated in infant pairs of twin-twin transfusion syndrome where blood pressures in recipients are significantly higher than donors (Mercanti et al. 2011). In fact, 14% of twin-twin transfusion recipients are hypertensive. And while it is common to find low blood pressure in neonates with blood stream infections, a recent study has shown that blood pressures actually increase in the days just prior to the clinical sepsis (Yapiciglu et al. 2015).

Not surprisingly, genetics also likely plays a role in which infants develop hypertension. Cytochrome P450 CYP2D6 "CC" genotype was associated with increased risk of elevated blood pressure in infants born less than 32 weeks of gestation during neonatal and follow-up periods (Dagle et al. 2011). All these various factors, including antenatal and postnatal exposures, gestational age, clinical condition, and genetic predisposition, probably interact in complex ways to influence neonatal blood pressures.

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 l of life (Zubrow et al. 1995). Their blood pressure nomograms have been the most widely used reference values. Similar to the blood pressure standards used in older children, the preference should be to use reference values determined from stable neonates as a better predictor of what is expected in healthy newborns. A more recent study of almost 400 hemodynamically stable infants has shown a similar correlation of gestational age and birth weight with blood pressure in neonates on day 1 of life, presented with 95% upper and lower confidence limits for ease of use (Pejovic et al. 2007) (see Fig. 1).

First Days of Life

In very low birth weight (VLBW) infants, systolic, diastolic, and mean blood pressures increase by more than 30% over the first few days of life which illustrates the significant physiologic changes that occur as neonates adapt to the extrauterine environment (Leflore et al. 2000). The mechanisms responsible for these dramatic changes are still being determined, but likely involve loss of vasodilator substances important during the in utero environment and maturation of factors controlling vascular tone (LeFlore et al. 2000; Joppich et al. 1979). The Philadelphia study showed that all infants in the NICU, regardless of gestational age, have a rapid increase in blood pressure over the first 5 days of life with increments around 1.5–2.5 mmHg/day (Zubrow et al. 1995). This differs from healthy term infants on the postnatal ward where blood pressure values are higher on day 2 compared to day 1 of life but not consistently thereafter (Kent et al. 2007a).

First Weeks of Life

In the first weeks of life, the rate of blood pressure change and the length of time over which the blood pressure is rapidly increasing may differ

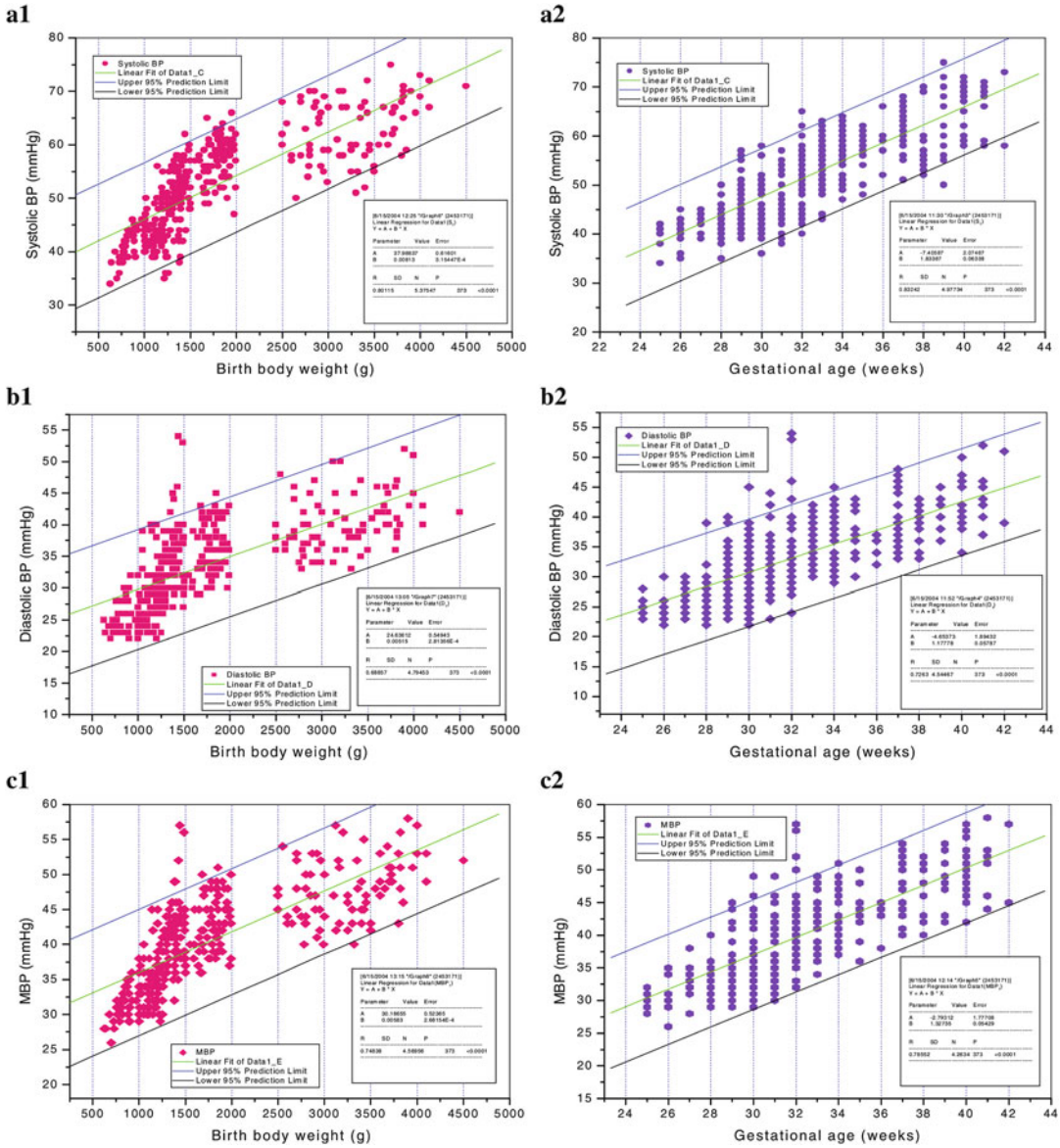

Fig. 1 Neonatal blood pressure on day 1 of life is positively correlated with birth weight (*1*) and gestational age (*2*). Systolic (**a**), diastolic (**b**), and mean (**c**) blood pressures are presented with 95 % confidence limits (Pediatric Nephrology, Blood pressure in non-critically ill preterm and full-term neonates, volume 22, 2007, pages 249–257, Pejovic B, Peco-Antic A, Marinkovic-Eric J, with permission of Springer)

based on gestational age at birth or birth weight. The study by Pejovic et al. (2007) found that the neonates with the lowest gestational age at birth had the most rapid rate of rise of blood pressure. In infants born at less than 28 weeks gestational age, the average increase in mean blood pressure was 26% in the first week and 51% in the first month compared to 13% and 22% in full-term infants. Another study of stable premature infants showed that the infants born at 28–31 weeks gestational age had a significant increase in blood pressure over the first 2–3 weeks of life, while the infants born at 32–36 weeks had a rapid increase over only 1 week (Kent et al. 2009a). The authors

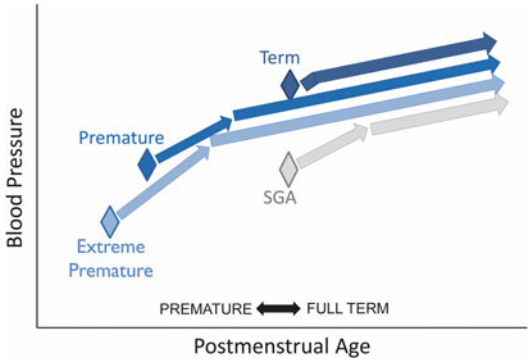

Fig. 2 Illustration of patterns of neonatal blood pressure changes when born at term or premature, extremely premature, or small for gestational age (*SGA*)

suggested that the blood pressure values at the end of the rapid increase were similar to term infants in the first days of life.

In the longer term, Georgieff et al. (1996) determined VLBW infants had similar blood pressure values to other NICU graduates at 4 months corrected age despite remaining smaller in length and weight. As blood pressures were not measured between discharge and 4 months of age, we do not know when the catch-up occurred. A study of full-term newborns found that the infants with the lowest birth weights, particularly the SGA infants, had the lowest blood pressures initially but then had the most rapid rate of rise of blood pressure (Lurbe et al. 2007). By 1 month of age, all term infants had similar blood pressures that remained comparable throughout the first year of life. The multitude of variations in blood pressure patterns over the first weeks of life is represented in Fig. 2.

Infant blood pressures have also been described as increasing with weight and with postmenstrual age. Lalan and Blowey (2014) recently derived a graph of intra-arterial MAP by postnatal weight with a slope showing that the MAP increased by 35 mmHg for every kilogram in weight gained. Zubrow et al. (1995) developed a clinically useful graphical reference of blood pressure increase by postconceptional age for neonates after the first day of life. Recognizing that infant blood pressures over the first 2 weeks are rapidly changing and could influence nomograms by postmenstrual age, Dionne et al. (2012) derived normative values for blood pressures after 2 weeks of life based on current postmenstrual age from the available published literature (see Table 2). Fiftieth, 95th, and 99th percentiles were calculated as a reference for clinicians.

First Year of Life

The blood pressure changes over the first year of life are less marked than in the newborn period. Blood pressure values increase steadily until 3–6 months of age at which time the values remain stable up to 1 year of age. The most widely used nomograms for infant blood pressure come from the Report of the Second Task Force on Blood Pressure from the National Heart, Lung, and Blood Institute (1987) (see Fig. 3). The infant blood pressures were measured using the Doppler method, which likely provides slightly lower readings than by the oscillometric method commonly used today. A more recent study of over 400 healthy term infants whose blood pressures were measured by oscillometric method shows a similar trend in blood pressure over the first year of life (Kent et al. 2007b). The blood pressures were only measured on day 2 of life and at 6 and 12 months of age and therefore do not provide normative data for ages in between. Large-scale studies of oscillometric blood pressure values over the first year of life are desperately needed.

Definition of Hypertension

Various definitions of infant hypertension have been used since high blood pressure was recognized as an issue in neonates and infants. This has made the comparison of studies and the determination of the incidence of hypertension challenging. Earlier studies used set blood pressure values for all term or preterm infants. As studies were published of normative values with percentiles, then clinicians applied the concept used in older children and adopted the 95th percentile blood pressure as the definition of hypertension.

Table 2 Infant blood pressures by postmenstrual age after 2 weeks of life; systolic blood pressure (SBP), mean arterial pressure (MAP), and diastolic blood pressure (DBP) are presented as 50th, 95th, and 99th percentiles

Postmenstrual age	Blood pressure	50th percentile	95th percentile	99th percentile
44 weeks	SBP	88	105	110
	MAP	*63*	*80*	*85*
	DBP	50	68	73
42 weeks	SBP	85	98	102
	MAP	*62*	*76*	*81*
	DBP	50	65	70
40 weeks	SBP	80	95	100
	MAP	*60*	*75*	*80*
	DBP	50	65	70
38 weeks	SBP	77	92	97
	MAP	*59*	*74*	*79*
	DBP	50	65	70
36 weeks	SBP	72	87	92
	MAP	*57*	*72*	*77*
	DBP	50	65	70
34 weeks	SBP	70	85	90
	MAP	*50*	*65*	*70*
	DBP	40	55	60
32 weeks	SBP	68	83	88
	MAP	*49*	*64*	*69*
	DBP	40	55	60
30 weeks	SBP	65	80	85
	MAP	*48*	*63*	*68*
	DBP	40	55	60
28 weeks	SBP	60	75	80
	MAP	*45*	*58*	*63*
	DBP	38	50	54
26 weeks	SBP	55	72	77
	MAP	*38*	*57*	*63*
	DBP	30	50	56

Adapted from Dionne et al. (2012)

Unfortunately, we do not have outcome studies in infants to support or refute the use of this arbitrary definition although in the future this may come from the neurocognitive or cardiovascular literature (Lande et al. 2003; Sharma et al. 2010). In addition, the use of antihypertensive medications in the neonatal and infant population can be associated with risks, and very few studies have been completed in this population. Therefore, at this time the best recommendation for definition of hypertension in neonates would be blood pressure values consistently above the 95th percentile based on postmenstrual age (see Table 2). In older infants, blood pressure values consistently above the 95th percentile based on curves from the Second Task Force on Blood Pressure (see Fig. 3) should be considered as hypertension and investigated and managed as appropriate.

Incidence of Hypertension

The incidence of hypertension in general healthy newborns is low, likely around 0.2%, and routine screening of blood pressure is not recommended (Ingelfinger 1982; Committee on Fetus and Newborn 1993). Blood pressures should be checked in infants considered "at risk" which includes NICU

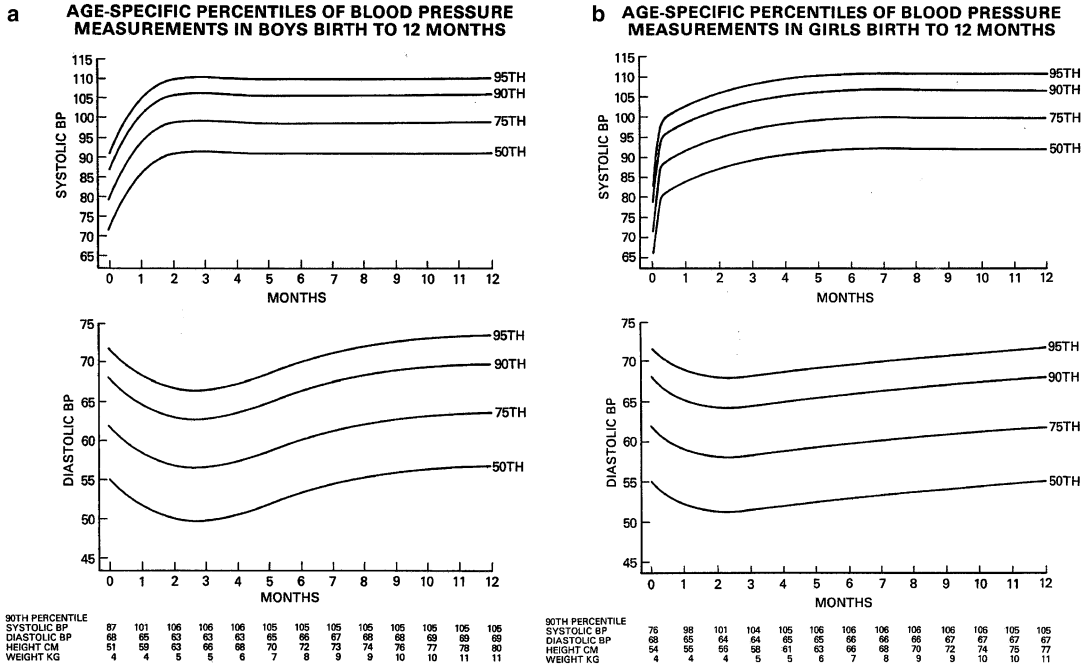

Fig. 3 Blood pressure percentiles for (**a**) male infants and (**b**) female infants from birth to 12 months of age (Reprinted from the Second Task Force on Blood Pressure Control in Children, National Heart, Lung, and Blood Institute (1987))

graduates, infants with congenital heart or kidney disease, or with other conditions known to affect blood pressure (4th Report 2004). In one of the first studies of neonatal hypertension, Adelman (1978) found an incidence of 2.5% in NICU infants when hypertension was defined as a blood pressure >90/60 mmHg in term infants or >80/45 mmHg in preterm infants. A recent large database study of more than 120,000 NICU encounters found an incidence of hypertension of 1.7% in all patients, and 1.0% after infants with congenital cardiac disorders were excluded (Blowey et al. 2011). Similarly, an Australian study of all newborns in a tertiary level NICU found an incidence of neonatal hypertension of 1.3% (Seliem et al. 2007). The median gestational age of these infants was 34 weeks, and the hypertension was diagnosed on average at postnatal day 5 although the range was 2–144 days. This is similar to an earlier study with a mean age of onset of 11 days suggesting that many infants that will develop hypertension do so within the first 1–2 weeks of life (Buchi and Siegler 1986). It is interesting that the incidence does not seem to be increasing despite the increasing complexity of patients within the NICU. It may be more likely that the incidence of hypertension in this population will be higher during adolescence and adulthood.

Risk Factors for Hypertension

Various factors have been associated with an increased risk for hypertension in neonates. It is important to recognize that risk factors may not be equivalent to causes as the data may come from sources where a primary cause of the hypertension was not able to be determined, as in a database, or multiple factors may have contributed to the development of hypertension in an individual patient. Also, the risk factor itself may not have been the cause of the hypertension but may be a surrogate for the state or condition of the infant. A recent study found that in preterm infants with hypertension, the etiology was more often related

to perinatal events, while in term infants with hypertension, an underlying cause was more likely to be found (Sahu et al. 2013).

Hypertension is more common in preterm infants and those with lower birth weights with as much as 75% of hypertension occurring in premature infants (Seliem et al. 2007; Sahu et al. 2013). The most commonly reported risk factors include umbilical artery catheters (UAC), chronic lung disease, and patent ductus arteriosus. Other risk factors include renal failure and congenital renal anomalies, intraventricular hemorrhage, steroids, and ECMO (Seliem et al. 2007; Singh et al. 1992; Blowey et al. 2011; Sahu et al. 2013). In a large database study by Blowey et al. (2011), the risk of hypertension was also higher in infants with neonatal asphyxia, seizures, and necrotizing enterocolitis and in those infants with a higher severity of illness score, more coexisting diagnoses, and in those that expired before discharge. Infants with hypertension seem to have a longer length of hospital stay which may be reflective of a more complex and ill population (Blowey et al. 2011; Sahu et al. 2013).

Causes of Hypertension

The most common causes of neonatal hypertension are renovascular and renal parenchymal disease, accounting for 25–50% of causes (Singh et al. 1992; Sahu et al. 2013). Cardiovascular causes are essential to diagnose early. The most common respiratory cause is chronic lung disease which may not present with hypertension until several months of age. Endocrine and neoplastic causes of hypertension are less common but important to diagnose as management is specific to each disease. Other causes are often iatrogenic such as pain, medications, and excess salt (see Table 3).

Renovascular Causes

The association between UACs and renal artery thrombosis has been recognized for decades. The mechanism is likely related to disruption of the vascular endothelium by the catheter with subsequent development of thrombus and clot extension or release of emboli. The incidence of clot formation associated with umbilical catheters differs widely depending on decade of screening and method of detection. An early study of randomly selected infants found a 95% incidence of clots associated with low thoracic UACs on aortograms (Neal et al. 1972). Seibert et al. (1987) studied neonates with lower placement of UACs and found 26% had an aortic thrombus by ultrasound, of which 29% were asymptomatic, 24% presented with hematuria, and 24% had hypertension. A recent Cochrane review of morbidity associated with UAC placement found high-placed UACs were associated with a lower incidence of clinical ischemic complications, but based on limited studies, it seems that hypertension and hematuria do not differ based on catheter position (Barrington 2010).

Renal artery thrombosis is most commonly associated with the use of UACs, and infants may present with a sudden increase in blood pressure. The incidence of hypertension in infants with a UAC has been reported between 1.6% and 8.8% (Blowey et al. 2011; Singh et al. 1992). In one study, 35% of hypertensive infants with a UAC had associated thrombocytopenia and 25% had lower limb ischemia (Singh et al. 1992). When investigating for this complication, it is important to realize that when clots are found, they are often extending into or originating from the aorta. Sometimes no clots will be found on imaging when the infant is hypertensive, suggesting either the clot has resolved, emboli occluded peripheral renal arteries, or the UAC caused renal arterial spasm or stenosis.

Renal vein thrombosis (RVT) classically presents with gross hematuria, a palpable abdominal mass, and thrombocytopenia and is often associated with hypertension and acute renal failure. Risk factors for RVT include birth asphyxia, maternal diabetes, hypovolemia, sepsis, and indwelling catheters. Most RVTs present within the first 3 days of life and over 70% are unilateral, with a preponderance for the left kidney and male infants (Lau et al. 2007).

Renal arterial stenosis may be a complication of a UAC, or it may be related to fibromuscular

Table 3 Causes of neonatal and infant hypertension

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
Patent ductus arteriosus	Hypercalcemia
Congenital ductus arteriosus aneurysm	Total parenteral nutrition
Congenital aortic aneurysm	Closure of abdominal wall defect
ECMO	Adrenal hemorrhage
Respiratory	Traction
Chronic lung disease	
Pneumothorax	

dysplasia, mid-aortic syndrome, or external compression by a mass. Less commonly in infants, it may be associated with a vasculitis or disease syndrome such as neurofibromatosis or Williams' syndrome. Other uncommon causes associated with renal artery stenosis include congenital rubella syndrome, renal myofibromatosis, and idiopathic arterial calcification of infancy (Mesner et al. 1966; Kasaragod et al. 1999; Milner et al. 1984). Renal artery stenoses are most commonly unilateral if idiopathic or related to catheters but more commonly bilateral if related to syndromes or other disease processes (see Fig. 4).

Renal Parenchymal Causes

Renal parenchymal causes may be intrinsic conditions such as polycystic kidney disease or renal dysplasia, may be related to urologic abnormalities such as ureteropelvic junction obstruction or obstructive uropathy, may be acquired conditions such as acute tubular necrosis or cortical necrosis, or rarely may be monogenic forms of hypertension. In hypertensive neonates within the NICU, between 25% and 40% will have a renal abnormality on ultrasound (Seliem et al. 2007; Singh et al. 1992). Lanzarini et al. (2006) studied nephro-urologic malformations in a tertiary care hospital and found an incidence of 0.89% in all infants, with almost 20% of affected neonates developing hypertension during the newborn period.

Congenital renal diseases associated with hypertension include polycystic kidney disease, renal dysplasia in isolation or associated with urologic abnormalities, and renal hypoplasia. Uncommon causes include multicystic dysplastic kidney, congenital or infantile nephrotic syndrome, renal tubular dysgenesis, or atypical hemolytic uremic syndrome. Autosomal recessive

polycystic kidney disease is more often presenting during the neonatal period in the recent decades (Guay-Woodford and Desmond 2003) (see Fig. 5). The median age at diagnosis of hypertension in these patients is 16 days old, and the hypertension may be challenging to treat requiring multiple agents. Even autosomal dominant polycystic kidney disease, where complications are less common during childhood, can cause hypertension in infants less than 1 year of age (Fick et al. 1993). Multicystic dysplastic kidneys rarely cause hypertension as they are thought to be nonfunctional but in some cases seem to cause severe hypertension, likely renin mediated, where the hypertension resolves after nephrectomy (Abdulhannan et al. 2011).

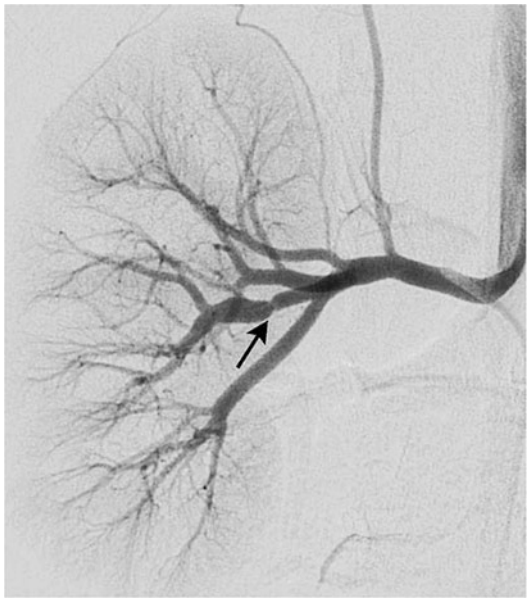

Fig. 4 *Renal angiogram* demonstrating renal artery stenosis of a second-order renal artery branch with poststenotic dilation (Pediatric Radiology, Anatomic distribution of renal artery stenosis in children: implications for imaging, volume 36, 2006, pages 1032–1036, Vo NJ, Hammelman BD, Racadio JM, Strife CF, Johnson ND, Racadio JM, with permission of Springer)

Renal dysplasia may be associated with hypertension and is common in obstructive uropathies such as posterior urethral value and prune belly syndrome. Renal dysplasia is often not seen in obstruction due to stones or tumors if the obstruction occurs after completion of renal development. Ureteropelvic junction obstruction has been associated with neonatal hypertension where correction of the abnormality is curative in most although infant pyeloplasty has also been related to a postoperative hyperreninemic hypertension (Gilboa and Urizar 1983). Other urologic abnormalities associated with infant hypertension include megaureter and neurogenic bladder, often in infants with a meningomyelocele.

Acquired renal causes of infant hypertension may include acute tubular necrosis related to moderate hypoxic, hypotensive, or nephrotoxic injury to the kidneys, or if more severe, kidneys may develop cortical necrosis. Other acquired causes of renal parenchymal disease and infant hypertension include pyelonephritis, interstitial nephritis, and nephrocalcinosis. Rare heritable forms of hypertension such as Liddle syndrome, apparent mineralocorticoid excess,

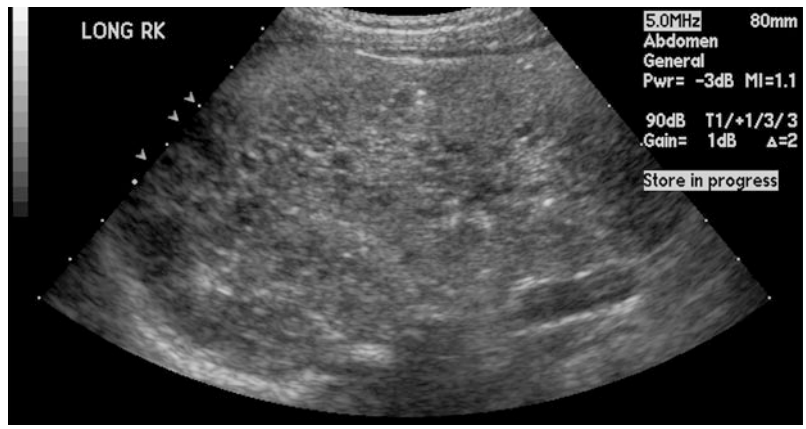

Fig. 5 *Renal ultrasound* image demonstrating an enlarged echogenic kidney with lack of corticomedullary differentiation and numerous microcysts consistent with autosomal recessive polycystic kidney disease

and glucocorticoid-remediable aldosteronism may present during infancy. Clinical suspicion based on family history and/or suppressed plasma renin can help diagnose these rare causes where treatments are directed at the specific underlying pathophysiology.

Cardiovascular Causes

Coarctation of the thoracic aorta may present with infantile hypertension and should be suspected in the presence of discrepant arm and leg pulses, perfusion, or blood pressures, especially with a cardiac murmur. Hypertension, as determined by a right upper arm blood pressure measurement, is present in 85% of children with aortic coarctation and persisted in 38% of infants after surgical repair (Smith Maia et al. 2004). This group is also at risk of restenosis and recurrent hypertension during childhood, with systolic blood pressure correlated with residual obstruction as a clue to persistent stenosis (O'Sullivan et al. 2002). Patent ductus arteriosus (PDA), closure of the PDA, and rarely congenital ductus arteriosus aneurysm have all been associated with neonatal hypertension (Murki et al. 2014). The mechanism of the PDA-related hypertension has been suggested to be renal microthrombosis with the PDA as the nidus, while closure of the PDA and hypertension could be related to the use of nonsteroidal anti-inflammatory drugs or the sudden increase in blood volume through the vessels.

ECMO deserves mention as a newer cause of infant hypertension as the technology becomes more widely utilized. An early study showed an incidence of 88% hypertension in infants on ECMO and 44% of infants developed intraventricular hemorrhage (Sell et al. 1987). In this study, 15% of infants still required some form of antihypertensive medication 1 month after ECMO. Other studies have found the incidence of hypertension to vary between 58% and 94 %, but fewer hypertensive infants (0–5%) developed intracranial hemorrhage (Boedy et al. 1990; Heggen et al. 2004). A review of 500 neonates treated with ECMO demonstrated that hypertension is the most common cardiovascular complication, occurring in almost 40% of infants, but when aggressively treated with vasodilators did not adversely affect survival (Becker et al. 1998). The mechanisms are thought to involve alterations in the baroreflex and modulation of hormones.

Other Causes

Chronic lung disease or bronchopulmonary dysplasia is another common cause of infant hypertension although it may present at neonatal follow-up clinics rather than during NICU admission. Of infants requiring home oxygen therapy for chronic lung disease, the incidence of hypertension during the first year of life has been reported from 13% to 43% with an average age of onset of 4–6 months (Anderson et al. 1993; Abman et al. 1984). Approximately half of cases occur after discharge from the NICU. In addition, some infants with chronic lung disease, or at risk of developing chronic lung disease, are treated with corticosteroids or other medications which can cause or exacerbate hypertension. The exact pathogenesis of the respiratory-related hypertension is unknown but may be related to chronic hypoxemia or hypercapnia, fluid retention, steroids or other medications, or alterations in vascular function or neurohormonal regulation.

Infant hypertension may also be found in disorders of the neurologic system. Pain and seizures may both lead to elevations in blood pressure, but management should be directed at the underlying stimulus, and antihypertensive medications will likely not be necessary. Intracranial hypertension may increase systemic blood pressure. Hypertension occurs in 2–3% of infants with intraventricular hemorrhage (Singh et al. 1992; Blowey et al. 2011). Unfortunately, the clinical signs of systemic hypertension and intraventricular hemorrhage may be indistinguishable and include irritability, lethargy, apnea, hypotonia, seizures, and coma (Adelman 1978). In these situations, appropriate imaging studies may evaluate for central nervous system causes or complications of the high blood pressure.

Although rare, the most commonly associated endocrine etiology for neonatal hypertension is congenital adrenal hyperplasia. Deficiencies in either 11β-hydroxylase or 17α-hydroxylase lead to overproduction of deoxycorticosterone which has mineralocorticoid activity. Other endocrine causes of hypertension include Cushing's syndrome, neonatal hyperthyroidism, hyperaldosteronism, and pheochromocytoma.

Several neoplastic causes of infant hypertension have been recognized including Wilms tumor, neuroblastoma, and mesoblastic nephroma which may all present during infancy. The mechanisms for the hypertension may include hyperreninemia related to renal parenchymal compression, renin release by the tumor, compression of the renal vasculature by the mass, or release of catecholamines by the tumor.

Various other causes of neonatal and infant hypertension have been recognized, many of which are iatrogenic. Certain medications or drugs may cause infant hypertension and may be prescribed to infants for a specific indication or related to maternal ingestion, as in cocaine or heroin abuse. Infants with chronic lung disease may be treated with corticosteroids, caffeine, or theophylline, all of which may lead to hypertension. Recent Cochrane reviews of early, moderately early, and late postnatal corticosteroids to prevent chronic lung disease found an increased risk of hypertension regardless of when the steroids were given (Doyle et al. 2014a, b; Halliday et al. 2003). Vitamin D intoxication has been associated with infant hypertension although it is not clear if this is related to hypercalcemia or some other mechanism. Excess saline administration or salt intake may increase blood pressures in neonates. Total parenteral nutrition has also been related to hypertension with the suspected mechanism either salt and water overload or hypercalcemia. Many of these iatrogenic causes of infant hypertension are based on clinically important indications, but when high blood pressures develop, the risk-benefit ratio must be reevaluated to determine if the medication or agent is still deemed essential.

Evaluation

Many infants with hypertension are asymptomatic, and common symptoms are often nonspecific such as feeding intolerance, vomiting, irritability, or failure to thrive. In those with more obvious symptoms, cardiovascular signs related to the blood pressure can include tachypnea, respiratory distress, and congestive heart failure. In some infants who present with cardiogenic shock, the elevated blood pressure is not detected until after the child is resuscitated and cardiac function improves (Xiao et al. 2013; Louw et al. 2013). Neurologic symptoms may be indistinguishable from intracranial hemorrhage and may include lethargy, apnea, tremors, opisthotonus, facial palsy, hemiplegia, seizures, and coma (Adelman 1978; Deal et al. 1992). Infants may be oliguric or polyuric with renal parenchymal or renovascular abnormalities (Ingelfinger 1982). Clinical signs and symptoms may provide clues to both the severity and the cause of the elevated blood pressure.

The infant's medical history should be reviewed for prenatal exposures, complications of delivery, perinatal course including use of invasive monitoring (umbilical lines), comorbid conditions, and current and previous medications. Family history may be helpful particularly when other infants have had complications in early life or when there is a history of hypertension at a young age. Fortunately, for premature infants, review of the patient chart often reveals the likely cause or several contributing factors to the development of the hypertension.

The initial step in physical assessment of the infant is to confirm the blood pressure elevation by using a standardized blood pressure measurement technique and ensuring the proper cuff size is used (see Table 1). Blood pressures and pulses should be assessed in all four limbs with discrepancies suggestive of coarctation, stenoses, or thromboses. The general condition of the infant should be noted including hydration status and dysmorphic features. Further examination should focus on the differential diagnosis (see Table 3) as well as look for signs of end organ damage including cardiac and neurologic abnormalities. Although procedurally challenging, signs of

Table 4 Diagnostic investigations for neonatal and infant hypertension

Common investigations	Specific investigations
Serum electrolytes (Na, K, Cl, HCO_3)	Plasma renin activity, aldosterone
Blood urea nitrogen, creatinine	Head ultrasound
Urinalysis	Serum calcium
Complete blood count	Cortisol, thyroid studies
Renal ultrasound with Doppler	Renal scintigraphy (MAG3, DTPA)
Echocardiography	Angiography

Na sodium, *K* potassium, *Cl* chloride, *HCO_3* bicarbonate, *DTPA-Tc 99m* diethylenetriaminepentaacetic acid, *MAG3-Tc 99m* mercaptoacetyltriglycine

hypertensive retinopathy may be present even in neonates with hypertension (Skalina et al. 1986). Abdominal examination is essential in these infants and should include inspection, auscultation for bruits, and palpation of the size and symmetry of the kidneys and for detection of masses.

Investigations should be tailored to the degree of hypertension and information gathered on history and physical examination. Basic laboratory investigations should include serum electrolytes, blood urea nitrogen, creatinine, urinalysis, and complete blood count (see Table 4). Renal ultrasound with Doppler is a high-yield initial investigation in this population. It is important to note that renal echogenicity and corticomedullary differentiation are relatively increased in neonates (Roth et al. 2003), and therefore interpretation should be conducted by radiologists with experience in pediatrics. Renovascular abnormalities may be suspected on ultrasound when there is abnormal renal size or echogenicity, with Doppler imaging better at identifying a thrombus or stenosis, although lack of vascular anomaly with Doppler ultrasound does not exclude a renovascular cause.

Echocardiography in infants with hypertension may help with diagnosis if cardiac abnormalities are identified but may also demonstrate evidence of target organ damage with left ventricular hypertrophy or congestive heart failure. Hypertension as a cause of heart failure in infants may be suspected by reduced left ventricular systolic function without chamber enlargement, increased left ventricular mass, diastolic dysfunction without left atrial dilatation, and aortomegaly with increased vascular resistance (Peterson et al. 2006; Louw et al. 2013). Infants may not be hypertensive at presentation when cardiac function is compromised but develop high blood pressure as cardiac function improves. Afterload reduction may improve both blood pressure and cardiac function (Peterson et al. 2006; Louw et al. 2013).

Plasma renin concentration or plasma renin activity may be difficult to interpret with limited normal reference values available for neonates. In addition, various measurements have been used including direct renin, plasma renin activity, and active renin mass with differences in normal values for the different assays. A newborn's renin is higher following a vaginal delivery and is higher in preterm than term infants (Kruger et al. 1998; Richer et al. 1977). In term infants, renin is highest in the first 4 days of life and then levels decrease over the following weeks to months to values similar to older children (Kruger et al. 1998). A suppressed plasma renin may be suggestive of a monogenic form of hypertension, while an elevated renin may suggest a renal artery stenosis or thrombosis. It is important to note that a normal plasma renin is common even in the presence of a renovascular abnormality so clinicians need to be aware of the limitations of this test as a screen for renovascular disease.

When renovascular hypertension is suspected, angiography may be the best investigation but is not always feasible. In children with renovascular hypertension without comorbid conditions, most will have a single stenosis with 75% occurring in a second-order or more distal branch artery (Vo et al. 2006) (see Fig. 4). Digital subtraction angiography is the most accurate for detection of arterial stenoses, and although it is invasive, it may be combined with differential renal vein renin sampling which may be helpful to localize the lesion and guide surgical management. Unfortunately, these procedures require a general anesthetic and may be technically challenging in small infants. Infants are often managed medically until they become an adequate size for the procedure. Other imaging techniques include computed tomography angiography or magnetic resonance angiography, although they are not as good at

detection of intrarenal vascular anomalies which are often present in infants (Roth et al. 2003). Consideration must also be given to a 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 (Kosch et al. 2004; Pergantou et al. 2014).

Management

Hypertensive Crises

Hypertensive crises are life-threatening emergencies that require prompt and careful management to avoid complications either of the hypertension or of the treatment. They are best managed within an intensive care setting with intravenous (IV) short-acting antihypertensive agents. Blood pressures should be reduced in a slow, controlled manner over days to avoid severe complications of relative hypotension (Deal et al. 1992). Several classes of antihypertensive agents have been used in infants for management of severe hypertension including vasodilators, ACE inhibitors, calcium channel blockers, and α- and β-antagonists (see Table 5).

Sodium nitroprusside has been used for decades in hypertensive crises and, due to the very short action of the medication, may be easily titrated to the desired effect. With prolonged use, infants need to be monitored for cyanide toxicity which can occur earlier in infants with renal failure. One case series of IV enalaprilat in neonates demonstrated a high incidence of side effects (Wells et al. 1990). Given the importance of the renin-angiotensin-aldosterone system (RAAS) in neonates, and lack of established dose, it cannot be recommended. Nicardipine, a dihydropyridine calcium channel blocker, has been used safely and effectively in premature and term infants with hypertension but requires administration through a central venous line and should be avoided in perinatal asphyxia (Milou et al. 2000; Flynn et al. 2001). Labetalol is a selective alpha-1-adrenergic antagonist and nonselective beta-adrenergic antagonist that has been used for decades to treat hypertensive crises. The efficacy and safety of IV labetalol is comparable to IV nitroprusside or IV nicardipine in infants less than 24 months of age (Thomas et al. 2011). Side effects of labetalol included hypoglycemia, bradycardia, and hypotension, and caution must be used in patients with preexisting brain injury. Esmolol, an IV cardioselective short-acting beta-antagonist, is a newer agent but has been used in children undergoing cardiac surgery for repair of congenital anomalies with good safety and efficacy (Wiest et al. 1998; Tabbutt et al. 2008).

Unfortunately, there are occasions when intravenous infusions are not immediately available and other agents must be used. Hydralazine may be given IV with a short onset of action of 5–20 min or orally with effect starting in 20–30 min. Nifedipine has been studied in infants with hypertensive crises at a dose of 2.5 mg with good effect (Lopez-Herce et al. 1989). Caution must be used with this medication as others have found transient neurologic changes in children and small doses require extraction of the liquid from a capsule with estimation of dose. Isradipine is a newer calcium channel blocker that is being used for acute hypertension as it is available in an immediate release formulation with onset of action of 30–60 min (Miyashita et al. 2010; Flynn and Warnick 2002). Other fast-acting medications to consider include oral captopril, clonidine, and minoxidil (see Table 5). Some of these agents may not be available in all locations, so one's choice of agent may be partly driven by what is available.

Non-emergent Hypertension

As with many medications in pediatrics, most antihypertensive drugs are not approved for use in infants, as adequate studies have not been conducted involving this age group. In neonates, the physiology of the immediate postnatal life is very different from older children, and therefore,

Table 5 Antihypertensive medications and recommended dosages for neonatal and infant hypertension

Drug class	Medication and route	Dose	Interval	Comments
Direct vasodilators	Sodium nitroprusside (IV)	Initial: 0.25 mcg/kg/min Max: 8 mcg/kg/min	Infusion	May cause hypotension, tachycardia. Monitor for cyanide toxicity. Caution in renal failure
	Hydralazine (IV) (PO)	0.2–1.0 mg/kg/dose 0.25–1.0 mg/kg/dose Max: 7 mg/kg/day	Q 4–6 h TID to QID	May cause tachycardia, fluid retention, diarrhea, emesis, agranulocytosis
	Minoxidil (PO)	0.1–1.0 mg/kg/day	BID	May cause tachycardia, fluid retention, hypertrichosis, pericardial tamponade, anorexia
ACE inhibitors	Captopril (PO)	Neonates Initial: 0.01 mg/kg/dose Max: 2 mg/kg/day Infants Initial: 0.1–0.3 mg/kg/dose Max: 6 mg/kg/day	BID to TID	May cause hypotension, oliguria, acute renal failure, hyperkalemia, neurologic complications
	Enalapril (PO)	Neonates: 0.04–0.1 mg/kg/day Infants: 0.08–0.6 mg/kg/day	Daily Daily to BID	All may cause hypotension, oliguria, acute renal failure, hyperkalemia, agranulocytosis, angioedema. Caution in preterm neonates
	Lisinopril (PO)	Infants: 0.07–0.5 mg/kg/day	Daily	
Calcium channel blockers	Nicardipine (IV)	0.5–4 mcg/kg/min	Infusion (central line)	May cause hypotension, tachycardia, and flushing. Caution in perinatal asphyxia
	Amlodipine (PO)	Initial: 0.05 mg/kg/dose Max: 0.6 mg/kg/day	Daily to BID	May cause edema, tachycardia, gingival hypertrophy
	Isradipine (PO)	Initial: 0.05–0.15 mg/kg/dose Max: 0.8 mg/kg/day	TID to QID	May cause hypotension, tachycardia, edema. Caution with QTc prolongation
	Nifedipine (PO)	0.1–0.25 mg/kg/dose Max: 2.5 mg	Q 4–6 h	May cause hypotension, tachycardia, transient neurologic changes
α- and β-antagonists	Labetalol (IV)	0.2–1.0 mg/kg/dose	Load	May cause hypotension, bradycardia, hyperkalemia, hypoglycemia, hyperglycemia, edema. Caution in chronic lung disease, heart block, unstable heart failure
		0.25–3.0 mg/kg/h	Infusion	
	Labetalol (PO)	1.0–10 mg/kg/day	BID	
	Carvedilol (PO)	0.05–0.4 mg/kg/dose	BID to TID	
β-Antagonists	Esmolol (IV)	50–1,000 mcg/kg/min	Infusion	All may cause hypotension, bradycardia. Caution in chronic lung disease, unstable heart failure
	Propranolol (IV)	0.01–0.15 mg/kg/dose	QID	
	Propranolol (PO)	0.25–5 mg/kg/day	TID to QID	
α-Antagonist	Prazosin (PO)	Initial: 5 mcg/kg/dose 0.05–0.5 mg/kg/day	TID	May cause hypotension, somnolence

(*continued*)

Table 5 (continued)

Drug class	Medication and route	Dose	Interval	Comments
Central 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	Daily to BID	May cause hyponatremia, hypokalemia, alkalosis
	Spironolactone (PO)	1–3 mg/kg/day	Daily to BID	May cause hyperkalemia. Caution in renal failure

ACE angiotensin-converting enzyme, *BID* twice daily, *IV* intravenous, *PO* oral, *QID* four times daily, *TID* three times daily

drug dosages and side effects can be quite different. Many older antihypertensive drugs have been used for decades to treat infant hypertension and are unlikely to be formally studied.

Captopril, a short-acting ACE inhibitor, is much more potent in neonates, and they require a lower dose for clinical effect (see Table 5). Infants may experience a significant decrease in blood pressure associated with captopril as well as acute renal failure and neurologic consequences (Perlman and Volpe 1989). Similar caution should be used for longer-acting ACE inhibitors such as enalapril and lisinopril when used in infants. In addition, we are learning more about the importance of the RAAS during renal development (Lacoste et al. 2006). Concerns have been raised about persistent use of inhibitors of this developmentally important system in neonates as long-term consequences have yet to be studied.

Amlodipine, a third-generation dihydropyridine calcium channel blocker, is generally safe and effective for management of childhood hypertension. It can be compounded in a suspension for use in young children and has a long half-life although may need to be dosed twice daily in younger children (Flynn and Pasko 2000). Isradipine, a second-generation dihydropyridine calcium channel blocker, has been used in hospitalized neonates, infants, and children with good effect (Miyashita et al. 2010; Flynn and Warnick 2002). Dosage based on size produced a relatively larger decrease in blood pressure in the infants compared to older children, but only 1% of patients developed clinically significant hypotension. Isradipine can be compounded into a stable suspension preparation improving its utility in neonates and infants.

α- and β-antagonists have been available and used for management of infant hypertension for decades but have been rarely studied in this population. The β-blocking side effects may include bradycardia, hyperglycemia, and hyperkalemia. Caution must be used in infants with chronic lung disease and heart block. Diuretics are used commonly in NICUs, often for indications other than blood pressure. They have modest effects on blood pressure reduction but may be first-line agents in infants with chronic lung disease or fluid retention. Electrolyte abnormalities are not uncommon and require laboratory monitoring.

Although most antihypertensive medications are not approved for use in infants, physicians have had to treat blood pressure with various agents to prevent the complications of uncontrolled hypertension. Hydralazine has been the most commonly used medication for neonatal hypertension since the 1970s. Other commonly prescribed agents include calcium channel blockers and ACE inhibitors with alpha- and beta-blockers less common but still of use (Seliem et al. 2007; Blowey et al. 2011; Sahu et al. 2013). Of interest, 30–50% of infants require more than one medication for blood pressure control, and this seems more common in term neonates. The hypertension may also be persistent with 40–85% of infants on antihypertensive medications at the time of discharge from the NICU. Of concern, in recent studies, 18–26% of identified hypertension

was not treated with any antihypertensive medications (Seliem et al. 2007; Blowey et al. 2011). The reasons were not identified but could be related to uncertainty in accurate diagnosis, lack of visible consequences of the hypertension, or unfamiliarity with antihypertensive medications, dosing, and side effects in neonates and infants.

In less than 10% of cases, surgical or interventional management can be curative for hypertension in infants (Sahu et al. 2013). For renal artery stenosis, percutaneous transluminal renal angioplasty to correct the stenosis may be curative when the lesion is unilateral although the procedure is technically more difficult in small infants who are often managed medically awaiting further growth. Surgical correction of coarctation of the thoracic aorta improves blood pressure in many but not all infants with this congenital malformation. For infants with tumors such as Wilms tumor, neuroblastoma, and mesoblastic nephroma, surgery usually results in normalization of the blood pressure. Rarely structural or function anomalies of the kidney and urinary tract associated with severe hypertension may require surgery. It has been reported as curative in some cases of ureteropelvic junction obstruction, multicystic dysplastic kidney, and unilateral renal hypoplasia (Munoz et al. 1977; Abdulhannan et al. 2011; Tokunaka et al. 1987). In exceptional circumstances, nephrectomy has been used for management of hypertension related to autosomal recessive polycystic kidney disease, which is often difficult to treat in infants, although may become easier with time (Roy et al. 1997).

Long-Term Outcome

Few follow-up studies of neonatal hypertension have been published. The review published by Adelman (1978) of 17 infants with neonatal hypertension found that 13 (76%) were normotensive off antihypertensive medications by 3–6 months after the onset. Results were similar in a slightly later study of NICU hypertensive infants where more than 50% were normotensive within the first month of life, two-thirds by 6 months of age, and more than 80% by 1 year of age (Buchi and Siegler 1986). In a recent Australian study of neonates with hypertension, more than 40% of infants were still receiving antihypertensive medications at discharge and 15% were still on treatment at follow-up at 3–6 months of age (Seliem et al. 2007). The vast majority seem to undergo resolution of their hypertension in the first 1–2 years of life (Shah et al. 2015).

While most neonatal hypertension improves with time, some conditions are associated with increasing rates of hypertension. Follow-up of infants with chronic lung disease has shown that half of the hypertension develops after NICU discharge and can last for up to 2 years (Anderson et al. 1993). In children with autosomal recessive polycystic kidney disease who survive the neonatal period, almost 40% require antihypertensive medications by 1 year, 50% by 3 years, and 60% by 15 years of age (Roy et al. 1997). Several long-term studies of renal vein thrombosis during infancy have found kidney outcomes are poor regardless of treatment with around 70% showing irreversible kidney damage at follow-up and about 20% of these patients had elevated blood pressure in the long term (Lau et al. 2007).

The recommendation of the 4th Report (2004) of the National High Blood Pressure Education Program is that children under 3 years of age only have their blood pressure measured at clinic visits if they have conditions associated with hypertension (e.g., cardiac or kidney disease) or if they were premature, VLBW, or NICU graduates. Sheftel et al. (1983) screened infants at follow-up clinics who were normotensive during their NICU course and found 9% were persistently hypertensive. After extending their cohort and follow-up period, they found 2.6% were hypertensive at an average follow-up of 19 months (Friedman and Hustead 1987). Causes identified included ureteropelvic junction obstruction, renal artery thrombosis, coarctation of the aorta, and neuroblastoma, but no cause was identified in the majority of children.

Neonatal Risk Factors for Later Renal and Cardiovascular Disease

It is becoming more widely recognized that perinatal events may alter risks for renal and cardiovascular disease in adolescence and adulthood.

A few comments are included here, but for a more detailed review, see ▶ Chap. 8, "Perinatal Programming of Arterial Pressure." In particular, there has been much focus recently on prematurity, intrauterine growth restriction, and postnatal weight gain as risk factors for future renal and cardiovascular disease. Although, there is still much controversy in the literature regarding which factors have a role and how much of an effect perinatal factors have compared to later health status.

The risks for development of hypertension in this population are likely multifactorial as these infants are often born prior to completion of nephrogenesis, at about 36 weeks gestation, and may be susceptible to acute kidney injury from hypoxia, hypotension, and nephrotoxins in addition to a possible genetic predisposition. Rodriguez et al. (2004) examined renal autopsy specimens from premature and term neonates and found that glomerulogenesis correlates with gestational age and is decreased in all preterm infants. In addition, active glomerulogenesis is absent in longer surviving premature infants and is further inhibited by acute kidney injury. Brenner et al. (1988) hypothesized that reduced nephron endowment predisposes to the development of hypertension through altered renal hemodynamics and reduced salt excretion (Brenner et al. 1988). They further postulated that with reduced nephron number, somatic growth can exceed renal growth and compensation mechanisms and one of the consequences may be hypertension (Mackenzie et al. 1996).

Studies that have followed up premature infants through childhood have found an increased incidence of hypertension, chronic renal insufficiency, and tubular dysfunction in this population (Kistvan Halthe et al. 2007). The renal dysfunction may be more marked in the presence of proteinuria and obesity (Abitbol et al. 2009). Using ambulatory blood pressure monitoring (ABPM), it was found that children born prematurely, particularly those that had intrauterine growth restriction, had higher nocturnal blood pressures and reduced dipping compared to controls (Bayrakci et al. 2007). Young adults who were born very premature (<32 weeks) or at very low birth weight (<1,500 g) have a very high rate of prehypertension (approx. 40%) and a higher prevalence of hypertension (approx. 10%) when compared to the general population of a similar age (Keijzer-Veen et al. 2005). As discussed above, hypertension may develop in children and adults who were born premature due to a reduced nephron endowment and maladaptive compensatory mechanisms.

Several studies have shown that low birth weight or being born small for gestational age is inversely correlated with blood pressure in childhood and early adulthood and is associated with a higher prevalence of hypertension (Hovi et al. 2010; de Jong et al. 2012; Zamecznik et al. 2014). A large cohort study including almost 30,000 children found that placental ratio percentage, as an indicator of intrauterine growth restriction, was a predictor of elevated blood pressure at 7 years of age while unadjusted birth weight was not (Hemachandra et al. 2006). ABPM studies in children born SGA have found blunted circadian and ultradian rhythms in addition to elevated blood pressures and hypertension when compared to appropriate birth weight children (Wolfenstetter et al. 2012; Zamecznik et al. 2014). Children and adolescents born SGA or growth restricted have lower elasticity of large and small blood vessels but a stronger vasodilatory response to ischemia compared to appropriate for gestational age children (Strambi et al. 2012). Differential vascular programming and altered cardiovascular regulation may be influencing later cardiovascular risks.

The role of early weight gain in later development of cardiovascular disease is still under debate. Studies have shown that accelerated infant weight gain during the first several months of life is related to higher systolic blood pressure as well as abnormal lipid profile and glucose metabolism during childhood and adolescence (Belfort et al. 2007; Fabricius-Bjerre et al. 2011; Lurbe et al. 2014). Another study of children who were born premature also showed that increased weight gain over the first year was associated with a slightly higher systolic blood pressure in childhood, but the weight gain was also associated with improved neurocognition (Belfort et al. 2010).

Several other studies have shown that early postnatal growth has an influence on childhood and early adulthood blood pressures but that the effect is small compared to later childhood growth or current body mass index (Keijzer-Veen et al. 2005; Law et al. 2002; Jones et al. 2012; Howe et al. 2014). This has led to the suggestion that the focus shift from perinatal growth to prevention of adiposity from later infancy through childhood as a more effective mechanism to reduce adulthood cardiovascular disease.

Conclusions

Neonatal and infant hypertension may be a challenging clinical issue, primarily because we are not certain of the definition of hypertension within this population and limited medication studies are available to guide treatment. Various factors, both intrinsic and extrinsic, can influence neonatal blood pressures with the strongest determinants being birth weight, gestational age, and postmenstrual age. Newer data on normal blood pressure values are available based on stable infants, but larger multicenter studies are needed to confirm and refine these reference values. The incidence of neonatal hypertension has remained fairly consistent over the last 30 years at 1–2% despite changes in the complexity of the neonatal population with new technologic advances. There seems to be a difference in the etiology of hypertension between preterm and term infants. Most causes or risk factors can easily be determined by assessment of the infant and some basic investigations. Neonatal hypertension is undertreated in the NICU and the reasons for this need further exploration. Most neonatal hypertension will resolve in the first 1–2 years although some disease states identified during infancy are associated with the development of hypertension over time. The exact impact of perinatal events on later renal and cardiovascular disease is still under investigation, but appropriate management of neonatal and infant hypertension is important for both the short- and long-term health of these infants.

Cross-References

- ▶ Development of Blood Pressure Norms and Definition of Hypertension in Children
- ▶ Management of Hypertensive Emergencies
- ▶ Methodology of Casual Blood Pressure Measurement
- ▶ Perinatal Programming of Arterial Pressure
- ▶ Pharmacologic Treatment of Pediatric Hypertension
- ▶ Renovascular Hypertension, Vasculitis, and Aortic Coarctation
- ▶ Secondary Forms of Hypertension in Children: Overview

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