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

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

Pediatric Hypertension

Second Edition

Humana Press

Pediatric Hypertension

Clinical Hypertension and Vascular Diseases

William B. White, MD
Series Editor

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Pediatric Hypertension

Second Edition

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ISBN 978-1-60327-823-2 e-ISBN 978-1-60327-824-9
DOI 10.1007/978-1-60327-824-9
Springer New York Dordrecht Heidelberg London

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Printed on acid-free paper

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Foreword

While hypertension in children and adolescents has a significant impact on adult cardiovascular disease as it transitions into adulthood, it also directly causes target organ damage and is associated with early atherosclerosis in children. The second edition of *Pediatric Hypertension* is an excellent reference textbook for any clinician or clinical researcher interested in this area as it provides a thorough review of what is known about childhood blood pressure based on the evidence from clinical studies, trials, and outcome research. The new edition has been substantially updated from the first edition of the book that was published in 2004—there are several new chapters and some old chapters have been modified or replaced. The second edition of *Pediatric Hypertension* is now a comprehensive textbook in 32 chapters that remain divided into 4 broad themes: (I) regulation of blood pressure and pathophysiology of hypertension in children; (II) assessment of blood pressure including measurement, normative data, and epidemiology; (III) definitions, predictors, risk factors, and comorbid conditions in childhood hypertension; and (IV) evaluation and treatment of hypertension in neonates and children.

As in the first edition of the book, the chapters are written by experts in their respective fields and remain nicely organized and easy to read and understand. The first section has been enlarged substantially and now includes chapters on vasoactive peptides, ion transport, and inflammatory mediators of vascular function. An excellent genomics chapter that was in edition 1 of the book has been moved into this section as well. The second section of the book now focuses not only on the epidemiology of hypertension in children but on cardiovascular diseases in general as well as on important comorbidities of obesity, diabetes, and metabolic syndromes in children and adolescents. The third section has also been expanded to encompass more in-depth discussion of perinatal programming, cardiovascular reactivity, and social environments as well as important clinical subpopulations of chronic and end-stage renal diseases and obstructive sleep apnea. In this second edition, there are also discrete new chapters on the impact of exercise on blood pressure and the utility of ambulatory blood pressure monitoring in assessing children with elevated blood pressure. The material in each chapter is presented in a logical 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.

It is pleasing to see the detail given in the section of the book on the management and treatment of hypertension in children. These chapters are destined to be very helpful for trainees in pediatrics and its subspecialties as well as practicing clinicians due to their pragmatic nature. The updated chapter on pediatric antihypertensive trials (Chapter 33) is particularly unique as it differentiates the issues of clinical trials for new antihypertensive medications in children versus adults and provides summary information from the US FDA.

As series editor of *Clinical Hypertension and Vascular Diseases*, I am highly enthusiastic about the second edition of *Pediatric Hypertension,* which I view as an extremely useful book that provides the most up-to-date and comprehensive review available on this

important topic. I expect that pediatricians, family medicine doctors, and all physicians with an interest in basic and clinical aspects of hypertension and its complications will find *Pediatric Hypertension* a valuable addition to their medical library.

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Preface to the Second Edition

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

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

It is also our hope that the advances summarized in this text will ultimately lead to increased efforts toward the prevention of hypertension in the young, which, in turn, should ameliorate the burden of cardiovascular disease in adults. We thank our many colleagues who have taken time from their busy schedules to contribute to this text—and we are sure that you will agree with us that their combined efforts have resulted in a valuable reference to those interested in hypertension in the young.

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I Regulation of Blood Pressure in Children

1 Neurohumoral Regulation of Blood Pressure in Early Development

Jeffrey L. Segar, MD

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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 in the fetus and newborn, although differential rates of maturation of these systems influence their ability to maintain blood pressure and delivery of oxygen and nutrients. This chapter focuses primarily on autonomic control of the fetal and newborn cardiovascular system and how hormonal and/or endocrine factors influence these systems.

Baroreceptor and chemoreceptor responses are vital for maintaining circulatory function. These neural pathways are modulated by a number of endocrine and paracrine factors, including angiotensin II (ANG II), arginine vasopressin (AVP), and corticosteroids. Understanding the neurohumoral mechanisms participating in cardiovascular regulation during the fetal and postnatal periods, particularly as they relate to the physiological adaptations occurring with the transition from fetal to newborn life, may ultimately result in new strategies to prevent complications during the perinatal period.

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_1
© Springer Science+Business Media, LLC 2011

OVERVIEW OF AUTONOMIC FUNCTION

Blood pressure is regulated through interacting neural, hormonal, and metabolic mechanisms acting within the brain, the end organs, and the vasculature. The central nervous system is critical for cardiovascular homeostasis, as cardiac and vasculature autonomic tone is continuously modulated by an array of peripheral sensors, including arterial baroreceptors and chemoreceptors *(1)*. Cardiovascular centers within the brain located between afferent and efferent pathways of the reflex arc integrate a variety of visceral and behavioral inputs, permitting a wide range of modulation of autonomic, cardiovascular, and endocrine responses. Developmentally regulated maturation of these basic systems in the fetus and newborn modulate the ability to maintain blood pressure and organ blood flow.

The contribution of the autonomic nervous system to cardiovascular homeostasis changes during development. Both α-adrenergic and ganglionic blockade, which inhibit sympathetic transmission at the ganglia and end organ, 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 high late in gestation *(2,3)*. The influence of the parasympathetic system on resting heart rate also appears to increase with maturation *(4)*. 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 *(3,5,6)*.

Arterial pressure displays natural oscillations within a physiological range, the degree of which is similar in fetal and postnatal life *(7–10)*. In the adult, ganglionic blockade increases arterial pressure variability *(7,11)*, suggesting that a component of arterial pressure lability is peripheral or humoral in origin and is buffered by autonomic functions. In contrast, ganglionic blockade in term fetal sheep significantly slows heart rate and attenuates arterial pressure variability *(9)*. Changes in fetal renal sympathetic nerve activity appear to correlate positively with fluctuations in heart rate and arterial pressure *(9)*. Although fetal electrocortical and sympathetic activity have not been recorded simultaneously, fetal heart rate, arterial pressure, and catecholamine levels are highest during periods of high-voltage, low-frequency electrocortical activity, suggesting that oscillations in sympathetic tone are related to changes in the behavioral state of the fetus *(12–15)*. Other physiological parameters, including organ blood flows, regional vascular resistance, and cerebral oxygen consumption, are also dependent on electrocortical state and likely reflect changes in autonomic activity *(12,16,17)*.

ARTERIAL BAROREFLEX

Arterial baroreceptors, 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. This increase in afferent nerve traffic, in turn, results in alterations in efferent parasympathetic and sympathetic nerve activities that influence heart rate and peripheral vascular resistance, serving to buffer changes in arterial pressure (Fig. 1) *(18,19)*. Baroreflex control of heart rate is dominated by changes in cardiac vagal tone, although integrity of the reflex is dependent upon both sympathetic and parasympathetic pathways *(20)*. Studies in animals demonstrate that the arterial baroreflex is functional during fetal and early postnatal life *(4,10,21,22)*. The observation that sinoaortic denervation produces marked fluctuations in fetal arterial pressure and heart rate further suggests important contributions of the baroreflex to cardiovascular homeostasis *(10,22)*.

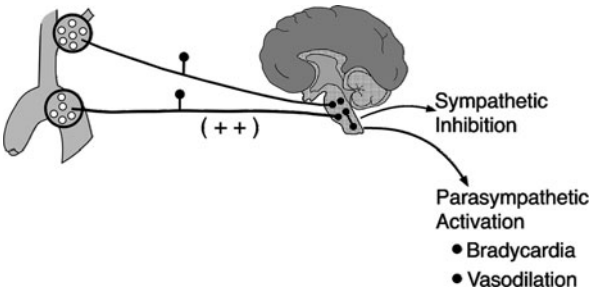

Fig. 1. Schematic representation of the arterial baroreflex, depicting how an increase in blood pressure modifies the discharge of afferent baroreceptor fibers located in the carotid sinus and aortic arch, which, in turn, results in alterations in efferent sympathetic and parasympathetic nerve activities that influence heart rate and peripheral vascular resistance, serving to buffer changes in arterial pressure.

Single-fiber recordings of baroreceptor afferents *(23–27)* in fetal and newborn 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 *(24–26)*. Basal discharge of baroreceptor afferents does not change during fetal and postnatal maturation, despite a considerable increase in mean arterial pressure during this time, indicating that baroreceptors reset during development, continuing to function within the physiological range for arterial pressure *(24,27)*. The sensitivity of carotid baroreceptors to increases in carotid sinus pressure is greater in fetal than in newborn and 1-month-old lambs *(24)* and in newborn as compared to adult rabbits *(27)*. These findings suggest that any reduced heart rate responses to changes in arterial pressure during fetal life (as discussed below) are not due to underdeveloped afferent activity of baroreceptors but rather 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 may strain sensitivity, ionic mechanisms that operate at the receptor membrane to cause hyperpolarization, or substances released from the endothelium, including prostacyclin and nitric oxide, that modulate baroreceptor activity *(28–33)*.

Many but not all studies in fetal and newborn animals describe baroreflex sensitivity, determined by the heart rate response to alterations in blood pressure, as being decreased early in development *(34–38)*. Using reflex bradycardia in response to increased blood pressure induced by balloon inflation, Shinebourne et al. *(36)* observed that cardiac baroreflex activity is present as early as 85 days of gestation (~0.6 of the length of gestation) in fetal lambs, and that the sensitivity of the reflex increased up to term. Heart rate responses to changes in blood pressure in the premature sheep fetus also appear to be asymmetric and are more sensitive to an increase than to a decrease in blood pressure *(39)*. In contrast to findings in sheep, the sensitivity of the cardiac baroreflex is greater in the horse fetus at 0.6 of the length of gestation than at near term (0.9 of gestation) *(40)*.

Developmental changes in the cardiac baroreflex continue postnatally. Heart rate responses to pharmacologically induced changes in blood pressure in fetal (135 ± 2 days of gestation (term=145 days)), newborn, and 4–6-week-old sheep demonstrated a trend for the sensitivity of the baroreflex control of heart rate to decrease with maturation *(41)*. However, further studies in sheep *(37)* and other species *(42,43)* reported 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 *(42)*. Age-related changes in heart rate in response to phenylephrine are also greater in 2-month-old piglets than in 1-day-old animals *(43)*. Differences in species, experimental conditions, and developmental changes in the innervation and functional contributions of the two arms of the autonomic nervous system (sympathetic and parasympathetic) likely contribute to these reported differences.

Baroreflex control of central sympathetic outflow, primarily measured as renal sympathetic nerve activity (RSNA), has been assessed as well. Booth et al. demonstrated in the preterm fetal sheep (at ~100 days or 0.7 of gestation) that baroreflex control of RSNA was absent although pulse synchronous bursts of RSNA were present *(39)*. Studies of the RSNA baroreflux function curve in late-gestation fetal (135 ±2 days gestation), newborn, and 4–6-week-old sheep indicated greatest sensitivity in the fetus and decreasing sensitivity during the postnatal period *(41)*. Interestingly, studies in aging animals have shown that baroreflex control of heart rate and sympathetic nerve activity is impaired with senescence *(44)*. Thus, the sensitivity of the baroreflex likely assumes an inverted "U" shape, increasing with early maturation, reaching a maximum sensitivity occurring during some developmental period, then decreasing 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 *(29,30)*. As already noted, studies indicate that the sensitivity of the baroreflex 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 *(45)*. 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 activity (central resetting) and at the end organ *(29)*. Locally produced factors, such as nitric oxide, and circulating hormones and neuropeptides, such as ANG II and AVP, activate additional neural reflex pathways that may modulate the changes in arterial baroreflex during development *(46)*.

Autonomic Function in the Developing Human

In the human infant, neural control of the circulation has been assessed most often 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 *(47–49)*. Using venous occlusion plethysmography, Waldman et al. *(49)* observed that healthy preterm and term infants subjected to 45° head-up tilting did not develop significant

tachycardia, although, on average, a 25% decrease in limb blood flow occurred, suggestive of an increase in peripheral vascular resistance. In contrast, Myers et al. reported 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 adults *(50)*. However, at 2–4 months of age the increase in heart rate to unloading of baroreceptors (head-up tilt) is lost *(50,51)*. One may speculate that this change may represent a vulnerable period of autonomic dysfunction and contribute to the risk for sudden infant death syndrome. Using noninvasive measurement of blood pressure sequences of spontaneous changes in blood pressure and heart rate in both premature and term infants (24 weeks gestational age to term), Gournay et al. reported that baroreflex sensitivity increased with gestational age and noted that sensitivity increased in premature infants (<32 weeks gestation), with postnatal age *(52)*.

Small, spontaneous beat-by-beat variations in heart rate may be analyzed as linear heart rate variability in both time and frequency domains and have been used in both infants *(53–55)* and fetuses *(56–58)* to evaluate the contribution of the autonomic nervous system in maintaining cardiovascular homeostasis. While the interpretation is considered somewhat subjective, analysis of fetal electrocardiogram tracings suggests differential development of the sympathetic and parasympathetic branches and progressive maturation of sympathovagal balance *(56–58)*. An increase in sympathetic tone appears around 32 weeks (0.8 of gestation), followed by moderation of sympathetic outflow related to the establishment of fetal behavioral states *(56)*.

Power spectral analysis is a technique used to characterize sympathetic and parasympathetic components of the heart rate, reported as a ratio of low-frequency (LF) to high-frequency (HF) components. In human infants, there is a progressive decline in the ratio of the low-frequency (LF) to high-frequency (HF) components with increasing postnatal and gestational age, indicating an increase in parasympathetic contribution to control of resting HR with maturation. In a small study of 24 sleeping infants, aged 31–41 weeks of conceptional age in which the babies were analyzed as 31–36-week, 37–38–week, and 39–41-week groups, Clairambault et al. *(55)* observed that changes in the HF component of the spectrum were greatest at 37–38 weeks, suggesting a steep increase in vagal tone at this age. 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 postconceptional age *(59)*. Longitudinal spectral analysis *(59)* indicated that the LF/HF ratio did not change with head-up postural change in infants at 28–30 weeks, whereas with increasing postnatal age the LF component of the spectrum increased with head-up tilt. In an elegant cross-sectional study of 1-week-old infants with postmenstrual ages ranging from 28 to 42 weeks, Andriessen observed increases in R–R interval, low- and high-frequency spectral powers, and baroreflex sensitivity with postmenstrual age *(53)*. Taken together, these observations suggest that neural regulation of cardiac function, particularly parasympathetic modulation, undergoes maturational change and becomes more functional with postnatal development.

CARDIOPULMONARY REFLEX

Cardiopulmonary receptors are sensory nerve endings located in the four cardiac chambers, in the great veins, and in the lungs *(60)*. In the adult, volume sensors mediating reflex changes in cardiovascular and renal function are believed to be primarily those residing in the atria *(61,62)* and the ventricles *(60)*. The ventricular receptors appear to be particularly important during decreases in cardiopulmonary pressures *(60,63,64)*. The majority

of ventricular receptor vagal afferents are chemosensitive and mechanosensitive (activated by changes in pressure or strength) unmyelinated C-fibers *(65,66)*. These receptors have a low basal discharge rate that exerts a tonic inhibitory influence on sympathetic outflow and vascular resistance *(60)* and regulates plasma AVP concentration *(67)*. Interruption of the basal activity of the vagal afferent receptors increases heart rate, blood pressure, and sympathetic nerve activity, whereas activation of cardiopulmonary receptors causes reflex bradycardia, vasodilation, and sympathoinhibition *(60)*.

Characterization of the cardiopulmonary reflex during the perinatal and neonatal periods was initially performed by stimulation of chemosensitive cardiopulmonary receptors *(43,68,69)*. Those studies demonstrated that the heart rate, blood pressure, and regional blood flow responses to stimulation of chemosensitive cardiac receptors were smaller early during development than later in life, and absent in premature fetal lambs *(68)* and in piglets under 1 week old *(69)*. 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 *(70,71)*. 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 *(72)*. 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.

Cardiopulmonary mechanoreceptors also respond to reductions in blood volume by eliciting reflexes that influence systemic hemodynamics. Gomez et al. observed 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 remained stable and heart rate increased in near-term fetuses *(73)*. However, other investigators *(74,75)* reported that the hemodynamic response to hemorrhage was similar in immature and near-term fetuses, with reductions in both heart rate and blood pressure. Inhibition of vagal afferents during slow, nonhypotensive hemorrhage blocked the normal rise in plasma AVP but did not alter the rise in plasma renin activity in near-term fetal sheep *(74)*. When input from cardiopulmonary receptors is removed by sectioning the cervical vagosympathetic trunks, the decrease in fetal blood pressure in response to hemorrhage is similar to that in intact fetuses *(76)*, whereas vagotomy with SAD enhances the decrease in blood pressure *(74)*. 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 RSNA in newborn lamb during nonhypotensive and hypotensive hemorrhage are dependent upon the integrity of arterial baroreceptors but not cardiopulmonary receptors *(77)*. In addition, the cardiovascular responses in newborn lambs to hemorrhage are dependent upon intact renal nerves that, in turn, modulate release of AVP *(78)*.

The RSNA responses to vagal afferent nerve stimulation are similar in sinoaortic-denervated fetal and postnatal lambs *(79)*, 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) is intriguing. One may suggest that there is an occlusive interaction between these two reflexes during development. In support of this hypothesis, studies in adults *(80,81)* have

shown 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 early postnatal life and participate in cardiovascular regulation *(82–84)*. Acute hypoxemia evokes integrated cardiovascular, metabolic, and endocrine responses in the fetus that result in transient bradycardia, increased arterial blood pressure and peripheral vascular resistance, and a redistribution of blood flow *(83,85)*. Oxygen sensing in the carotid body is transduced by glomus cells, which are 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 that generate an action potential in the carotid sinus nerve *(86)*. The bradycardia associated with hypoxemia is mediated by parasympathetic efferents, while the initial vasoconstriction results from increased sympathetic tone *(84,87)*. 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 via either umbilical cord occlusion or administration of subambient oxygen to the ewe *(84,88–91)*. Responses to moderate hypoxemia appear attenuated in preterm fetuses, possibly related to lower aerobic requirements. However, responses to prolonged asphyxia, induced by umbilical cord occlusion, are comparable in preterm, mid-term, and near-term fetuses, although the rapidity and intensity of peripheral vasoconstriction were attenuated in the younger animals *(91)*. The cardiovascular response to acute fetal hypoxemia depends upon the intrauterine milieu *(85, 92–94)*. For example, 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 *(94)*. Such strong responses likely resulted from acidemia-mediated sensitization of the carotid body, increased sympathetic outflow and stimulation, catecholamine secretion. To examine the effects of prevailing hypoxemia on responses to acute hypoxemia, Gardner et al. *(85)* studied chronically instrumented fetal sheep, which were 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 hypoxic fetuses relative to control fetuses. Additional evidence suggests that exposure to hypoxia for a limited periods of time (hours to days) has a sensitizing effect on the chemoreflex, whereas more sustained hypoxia (days to weeks) may have a desensitizing effect *(93)*. 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 *(95)*. 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 *(96)*. 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 *(97,98)*. This decreased sensitivity persists for several days until the chemoreceptors adapt and reset after emerging from the low oxygen tension of the fetus to the higher levels seen postnatally *(98,99)*. The mechanisms involved with this resetting are not known, although the postnatal rise in PaO_2 appears crucial, since raising fetal PaO_2 produces a rightward shift in the response curve of carotid baroreceptors to differing oxygen tension *(100)*. Potential mechanisms within the glomus cells regulating developmental changes in O_2 transduction and chemoreceptor responses include, but are not limited to, anatomic maturation, developmental changes in oxygen-sensitive K^+ currents, adenosine responsiveness *(101,102)*, dopamine and catecholamine turnover within the carotid body *(103)*, and differences in intracellular calcium mobilization during hypoxia *(86,104)*.

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 *(105,106)*. Activation of the sympathetic nervous system appears to be important in this adaptive process and is associated with marked increases in circulating catecholamines *(107,108)*. Arterial pressure, heart rate, and cardiac output are all depressed by ganglionic blockade in newborn (1–3 days) but this does not occur in older lambs, suggesting that sympathetic tone is high during the immediate postnatal period *(109)*. Our group has demonstrated that 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 *(45)*. Delivery appears to produce near-maximal stimulation of renal sympathetic outflow, since further increases cannot be elicited by unloading of arterial baroreceptors *(45)*. 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 *(41)*, suggesting that central influences can 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 *(110)*.

The factors that mediate the increase in sympathetic outflow at birth are incompletely understood. 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 *(111,112)*. 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 *(113)*, 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 in fetal lambs that have undergone both sinoaortic denervation and vagotomy *(114)*, demonstrating that afferent input from peripheral chemoreceptors and mechanoreceptors also contributes 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 either in utero or in exteriorized preparations results in an increase in heart rate, blood pressure, and norepinephrine concentrations, consistent with sympathoexcitation *(115,116)*.

In contrast, exteriorization of the near-term lamb fetus into a warm water bath does not produce the alterations in systemic hemodynamics or catecholamine values typically seen at birth *(116)*. Fetal cooling, but not ventilation or umbilical cord occlusion, initiates nonshivering thermogenesis via neurally mediated sympathetic stimulation of brown adipose tissue *(117)*. In utero cooling of fetal lambs also produces an increase in RSNA of similar magnitude to that seen at delivery by cesarean section *(49)*, 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 occurs, 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.

Studies in adults suggest that multiple brain centers are involved in autonomic control of the systemic circulation. Sympathetic outflow is controlled not only by the medulla oblongata *(118)*, but also by higher centers, especially the hypothalamus *(119–121)*, allowing for a wide range of modulation. Neuroanatomic 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 *(119–121)*. How the supramedullary regions influence cardiovascular function in developing animals is unclear. In fetal sheep, electrical stimulation of the hypothalamus evokes tachycardia and a pressor response, both of which are attenuated by α-adrenoreceptor blockade *(122)*. Stimulation of the dorsolateral medulla and lateral hypothalamus in the newborn piglet similarly increases blood pressure and femoral blood flow *(43)*. 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 *(43)*. However, other studies suggest that 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 that normally occur at birth are absent in animals subjected to transection of the brain stem at the level of the rostral pons prior to delivery *(113)*. Ablation of the paraventricular nucleus of the hypothalamus in fetal sheep attenuates the postnatal increase in sympathetic outflow and alters baroreflex function *(123)*. 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 (about 123 days)) compared to those delivered at term *(124)*. Postnatal increases in heart rate and blood pressure are attenuated, and the sympathoexcitatory response, as measured by RSNA, is absent *(124)*. This impaired response occurs despite the fact that 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 *(124)*. Antenatal administration of glucocorticoids, which has been shown to improve both postnatal cardiovascular and pulmonary functions, augments sympathetic activity at birth in premature lambs and decreases the sensitivity of the cardiac baroreflex *(124)*. The mechanisms through which antenatal glucocorticoid administration augments cardiovascular and sympathetic responses at birth are unclear, although stimulation of the peripheral renin–angiotensin system and activation of peripheral angiotensin receptors appear not to be involved *(125)*.

HUMORAL FACTORS

Renin–Angiotensin System in the Fetus and Neonate

The renin–angiotensin system is active in the fetal and perinatal periods *(126–128)*. 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 *(129)*. Only later during fetal development does the renin–angiotensin system become involved in modulating cardiovascular function and renal hemodynamics. A large number of studies report that administration of inhibitors of ANG II, including angiotensin-converting enzyme inhibitors (ACEi's) and angiotensin II subtype 1 receptor blockers (AT_1 blockers, or ARBs), decreases fetal and newborn arterial blood pressure *(127,130–132)*. In normal children, plasma renin activity is high during the newborn period, declines rapidly in the first year of life, and then continues with a gradual decline until adulthood *(133,134)*. In preterm infants, plasma renin activity is markedly elevated and has close inverse relationship to postconceptual age *(135)*.

Fetal plasma renin activity and plasma ANG II concentration increase after aortic constriction, hypotension, and blood volume reduction *(126)*. Conversely, a rise in arterial blood pressure and volume expansion reduce plasma renin activity in fetal and newborn animals *(136)*. The vasopressor response and renal vascular reactivity to exogenous ANG II are less in fetal lambs than in adult sheep *(137)*. Factors explaining the higher activity of the renin–angiotensin system early in development but decreased sensitivity to ANG II have not been explored in detail. 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 *(46,138)*, changes in the levels of these circulating hormones, in turn, influence neural regulation of cardiovascular function. For example, in the sheep fetus, a rise in arterial blood pressure produced by ANG II administration produces little or no cardiac slowing *(137,139)*, although others have reported dose-dependent decreases in heart rate *(140,141)*. The bradycardic and sympathoinhibitory responses to a given increase in blood pressure are less for ANG II than for other vasoconstrictor agents *(142)*. In the adult ANG II facilitates activation of sympathetic ganglia and enhances the release of norepinephrine at the neuroeffector junction *(143)*. Within the central nervous system, ANG II stimulates sympathetic outflow and alters baroreceptor reflexes by acting on AT_1 receptors located within the hypothalamus, medulla, and circumventricular organs *(144–146)*. 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 *(147–149)*. 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 *(147–149)*. Lateral ventricle administration of an AT_1 but not an ANG II receptor subtype 2 (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 *(150)*.

Endogenous circulating ANG II participates in regulating arterial baroreflex responses early during development. The absence of rebound tachycardia after reduction in blood pressure by ACEi is well described in fetal and postnatal animals *(130)*, as well as in human adults and infants *(54)*. 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 *(142,150)*. Resetting of the reflex is independent of changes in prevailing blood pressure.

Arginine Vasopressin in the Fetus and Neonate

Several lines of evidence suggest that arginine vasopressin (AVP) plays an important role in maintaining cardiovascular homeostasis during fetal and postnatal development. Plasma AVP concentrations in the fetus are increased by multiple stimuli, including hypotension, hemorrhage, hypoxemia, acidemia, and hyperosmolality *(138, 151–153)*. 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 *(154,155)*. Infusion of AVP increases fetal blood pressure and decreases fetal heart rate in a dose-dependent manner *(156,157)*, although AVP appears to have little 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 *(158,159)*. However, AVP receptor inhibition impairs the ability of the fetus to maintain blood pressure during hypotensive hemorrhage and reduces the catecholamine response *(160)*.

In several adult mammalian species, AVP modulates parasympathetic and sympathetic tone and baroreflex function *(46,159,161,162)*. Administration of AVP evokes more sympathoinhibition and bradycardia than other vasoconstrictors at a comparable increase in blood pressure *(46,162)*. It has been thought that such baroreflex modulation by AVP is due to enhanced baroreflex gain and resetting of the baroreflex to a lower pressure *(46,162)*. 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 *(159)*.

Endogenous AVP also appears to have little effect on baroreflex function early during development. For instance, peripheral intravenous administration of a V_1-receptor antagonist has no measurable effects on resting hemodynamics in fetal sheep or on basal arterial blood pressure *(158)*, heart rate, RSNA, or baroreflex response in newborn lambs *(159)*. This lack of baroreflex modulation by AVP may facilitate the observed pressor response to AVP in fetuses and newborns during stressful situations such as hypoxia and hemorrhage. Such responses suggest that AVP could play a particularly important role in maintaining arterial pressures during stressful states in early development.

The role of AVP within the central nervous system 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 that AVP contributes to the central regulation of autonomic function (163). Intracerebroventricular infusion of AVP produces significant decreases in mean arterial blood pressure and heart rate in newborn lambs without reflex changes in RSNA *(164)*. In contrast, intracerebroventricular administration of AVP increases RSNA in 8-week-old sheep, demonstrating that the role of AVP receptors within the CNS in regulation of autonomic function is developmentally regulated *(164)*. The changes in blood pressure and heart rate are completely inhibited by administration of a V_1 antagonist, demonstrating that the central cardiovascular effects of AVP are mediated by V_1 receptors, as has been reported in mature animals *(165)*.

Corticosteroids in the Fetus and Neonate

The prepartum surge in fetal cortisol levels, observed 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 *(166,167)*. Antenatal exposure to exogenous glucocorticoids increases fetal and postnatal arterial blood pressure by enhancing peripheral vascular resistance and cardiac output without altering heart rate *(168–170)*. The effectiveness of hydrocortisone for treatment of hypotension in preterm and term neonates is well described *(171,172)*. However, the mechanisms by which glucocorticoids increase blood pressure and vascular resistance in this age group 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 *(173,174)*. On the other hand, glucocorticoids enhance pressor responsiveness and vascular reactivity to norepinephrine and ANG II *(175,176)*, in part by increasing α_1-adrenergic and AT_1 receptor levels and potentiating ANG II- and AVP-induced inositol triphosphate production *(177,178)*. 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 *(179)*.

In the sheep fetus, cortisol infusion increases blood pressure, as well as the hypertensive response to intravenous ANG II but not to norepinephrine *(166)*. However, infusions of synthetic glucocorticoids, which also increase arterial blood pressure, do not alter the pressor response to phenylephrine, ANG II, or AVP *(180)*. Furthermore, the increase in blood pressure is not inhibited by blockade of the renin–angiotensin system *(125)*. 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 *(181)*. 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 *(181–184)*.

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 *(124,168,185)*. Circulating neuropeptide Y concentration, which may provide an index of peripheral sympathetic activity, is increased following fetal exposure to dexamethasone *(186)*. Glucocorticoid treatment accelerates postnatal maturation of brain catecholaminergic signaling pathways in rats and enhances renal sympathetic nerve activity in prematurely delivered lambs *(71,187,188)*.

Endogenous production of cortisol is important for normal maturational changes in autonomic reflex function. Adrenalectomized fetal sheep fail to display the normal postnatal increase in RSNA, while the response is restored by cortisol replacement *(189)*. 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 *(189)*. Antenatal administration of betamethasone decreases the sensitivity of baroreflex-mediated changes in heart rate in preterm fetuses and premature lambs *(124)*. Antenatal glucocorticoid exposure also alters baroreflex and chemoreflex function in fetal and newborn animals *(180,187)*. Baroreflex control of heart rate and RSNA

are reset toward higher pressures in steroid-exposed animals. In response to acute hypoxia, fetuses exposed to exogenous corticosteroids display prolonged bradycardia and attenuated plasma catecholamine and AVP responses *(186)*. Consistent with this finding, ovine fetuses at >140 days gestation (term 145 days) and with naturally elevated cortisol levels displayed greater heart rate, vasoconstrictor, and neuroendocrine responses to hypoxemia than fetuses at 125–140 days gestation *(92)*. At all gestational ages the responses to hypoxemia correlated with the prevailing cortisol concentration. Taken together, these findings indicate that corticosteroids modify autonomic and endocrine control of cardiovascular function during development. These effects may even persist well after cessation of exposure *(186)*.

Nitric Oxide in the Fetus and Neonate

Nitric oxide (NO) plays an important role in the control of systemic hemodynamics early in development. Nitric oxide regulates fetal vascular tone, blood pressure, and organ-specific vascular resistance. Inhibition of NO production causes an immediate rise in blood pressure and umbilicoplacental resistance, and decreases in heart rate, renal blood flow velocity, and plasma renin concentration *(190–192)*. These cardiovascular effects are significantly attenuated by prolonged or repeated exposure to NO synthesis inhibition, indicating that other vasodilatory regulatory mechanisms are functioning during fetal life *(190)*. Nitric oxide also functions as a neurotransmitter and acts centrally to regulate fetal arterial blood pressure. Administration of the NO donor, nitroglycerin, into the fourth cerebral ventricle of the ovine fetus decreases mean arterial pressure, whereas blocking NO synthase in the fourth ventricle increases fetal blood pressure *(193)*. Inhibition of endogenously produced NO also increases blood pressure in 1- and 6-week-old lambs to similar extents, although the concomitant decreases in heart rate are greater in the young lamb *(194)*. Endogenous nitric oxide regulates arterial baroreflex control of heart rate in 1-week-old but not 6-week-old lambs and may contribute to developmental changes in baroreflex function during this period *(194)*.

CONCLUSIONS

Understanding the mechanisms regulating cardiovascular function in the fetal and postnatal periods, particularly as they relate to the transition from fetal to newborn life, 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 important modulators of blood pressure and circulatory function early in life. Humoral and endocrine factors, not only those discussed above, but others such as opioids, natriuretic peptides, and prostanoids, act directly and indirectly to regulate vascular tone and cardiac function. A more complete understanding of neurohumoral control of cardiovascular function early in life may potentially lead to the development of new therapeutic strategies to prevent complications during the perinatal period.

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2 Vasoactive Factors and Blood Pressure in Children

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CONTENTS

INTRODUCTION

Vasoactive peptide systems play a critical role in the regulation of arterial blood pressure (BP). Inappropriate stimulation or deregulation of cross talk between diverse vasomotor factors contributes in a major way to the development of hypertension, cardiovascular disease, and renal disease in children. Understanding how derangements in vasoactive factor systems may lead to these health problems might potentially prevent disease from occurring. This chapter will review new advances in physiology, biochemistry, pathophysiology,

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_2
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and function of the renal and systemic vasoactive systems with special emphasis on their role in the pathogenesis of hypertension in children.

THE RENIN–ANGIOTENSIN SYSTEM

The renin–angiotensin system (RAS) plays a fundamental role in the regulation of arterial BP. Emerging evidence suggests that many tissues have a local tissue-specific RAS, which is of major importance in the regulation of the angiotensin (Ang) levels within many organs *(1, 2)*. The RAS includes multiple components. The enzyme renin cleaves the substrate, angiotensinogen (AGT), to generate Ang I [Ang-(1–10)] (Fig. 1). Ang I is converted to Ang II [Ang-(1–8)] by angiotensin-converting enzyme (ACE). ACE expression on endothelial cells of many vascular beds including those in the kidney, heart, and lung allows systemic formation of Ang II, the most powerful effector peptide hormone of the RAS, throughout the circulation *(3–5)*. Most of hypertensinogenic actions of Ang II are attributed to the AT_1 receptor (AT_1R) *(6)*. Additionally, there are further pathways by which angiotensins may be formed—Ang II via chymase in tissues and Ang II metabolites via ACE2, as well as via endopeptidases.

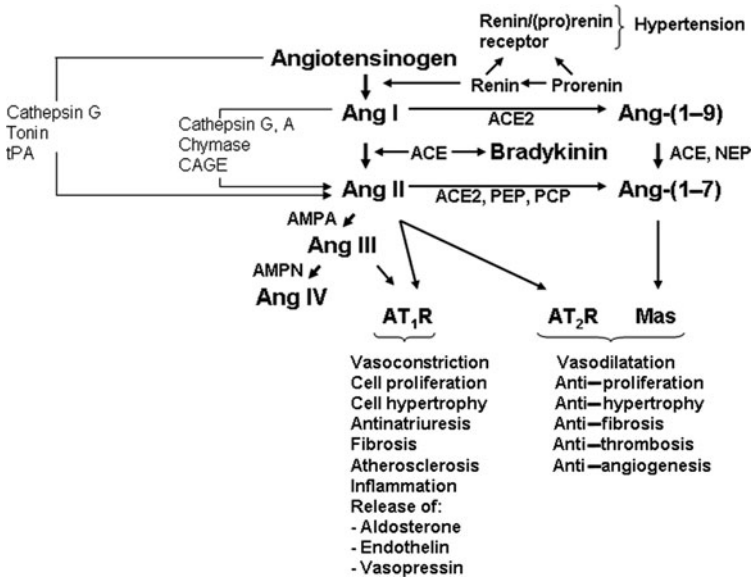

Fig. 1. Renin-Angiotensin System, with focus on target effects of Angiotensin II and alternate pathways of Angiotensin metabolism.

ANGIOTENSINOGEN

Angiotensinogen (AGT) is formed and constitutively secreted into the circulation by the hepatocytes *(7)*. In addition, AGT mRNA and protein are expressed in kidney proximal tubules, central nervous system, heart, adrenal gland, and other tissues *(8,9)*. Although AGT is the only substrate for renin, other enzymes can cleave AGT to form Ang I or Ang II (Fig. 1) *(10,11)*. Expression of the AGT gene is induced by Ang II, glucocorticoids, estrogens, thyroxine, and sodium depletion *(9,12,13)*.

A number of AGT polymorphisms appear to influence BP level. For example, an A/G polymorphism at −217 in the promoter of the AGT gene may play an important role in hypertension in African-Americans *(14)*.

PRORENIN, RENIN, AND (PRO)RENIN RECEPTOR

The major site of renin synthesis is in the juxtaglomerular cells of the afferent arterioles of the kidney, first as preprorenin *(15)*. The human renin gene, which encodes preprorenin, is located on chromosome 1 *(16)*. Cleavage of a 23-amino acid signal peptide at carboxyl terminus of preprorenin generates prorenin. Prorenin is then converted to active renin by cleavage of 43-amino acid N-terminal prosegment by proteases *(5,17)*. The kidney secretes both renin and prorenin into the peripheral circulation. Plasma levels of prorenin are approximately tenfold higher than those of renin *(18)*. Renin release is controlled relatively rapidly by baroreceptors in the afferent arterioles, 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) *(19–22)*. 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) *(23–25)*. In contrast, changes in AGT synthesis occur relatively slowly and thus are less responsible for the dynamic regulation of plasma Ang I and Ang II than changes in renin *(3,26)*. In addition, the circulating concentrations of AGT are more than 1000 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 *(10,11)*, the circulating levels of Ang II reflect primarily the consequences of the action of renin on AGT *(27)*.

Recently, the renin/prorenin–(pro)renin receptor complex has emerged as a newly recognized pathway for tissue Ang II generation. In addition to proteolytic activation, prorenin may be activated by binding to (pro)renin receptor *(28)*.

The (pro)renin receptor is expressed on mesangial and vascular smooth muscle cells and binds both prorenin and renin *(29)*. Binding of renin or prorenin to (pro)renin receptor induces a conformational change of prorenin, facilitating catalytic activity and the conversion of AGT to Ang I *(28)*. A direct pathological role of the (pro)renin receptor in hypertension is suggested by the findings of elevated blood pressure in rats with transgenic overexpression of the human (pro)renin receptor *(30)*.

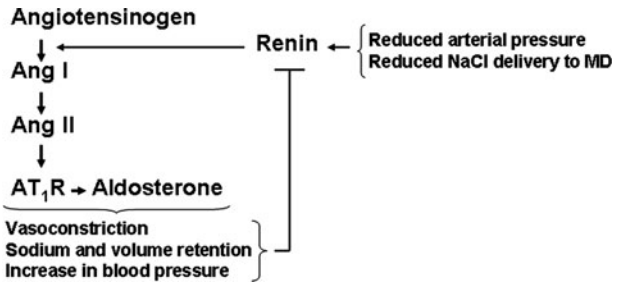

Fig. 2. Feedback loop between renin secretion and end-effects of the renin-nagiotensin-aldosterone system.

ANGIOTENSIN-CONVERTING ENZYME

Angiotensin-converting enzyme (ACE) is involved in the posttranslational processing of many polypeptides, the most notable of which are Ang I and bradykinin (BK) (Figs. 1 and 3). There are two ACE isozymes, somatic and testicular, transcribed from a single gene by differential utilization of two distinct promoters *(31)*. 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 an ectoenzyme in glomerular vascular endothelial and proximal tubular cells *(32)*. 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. Polymorphisms in the ACE gene appear to be important in blood pressure regulation. In particular, an insertion/deletion (I/D) polymorphism of 287 base pairs in exon 16 is associated with hypertension *(33)*. Persons with the D allele have higher plasma ACE levels and higher rates of hypertension.

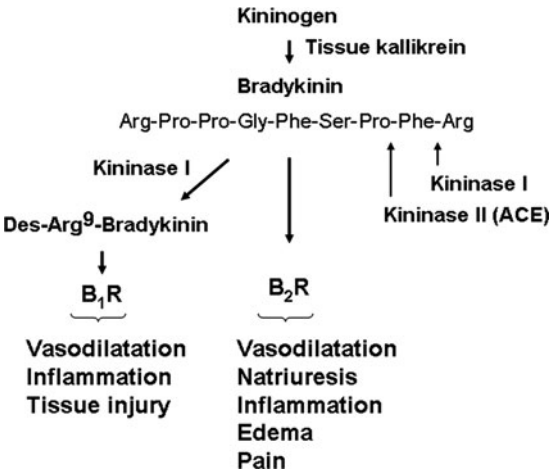

Fig. 3. Bradykinin-kinase system with focus on end-effects of bradykinin and its degredation products.

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 *(34)*. 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 *(35)*. Activation of Ang II binding to the AT_1R increases BP by (1) direct vasoconstriction and increase in peripheral vascular resistance; (2) stimulation of Na reabsorption via the sodium hydrogen exchanger 3 (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 (3) stimulation of aldosterone biosynthesis and secretion by the adrenal zona glomerulosa (Fig. 2) *(36–38)*. AT_1R activation also stimulates vasopressin and endothelin secretion and stimulates the sympathetic nervous system, and the proliferation of vascular smooth muscle and

mesangial cells *(39–41)*. The AT_2R has 34% homology with AT_{1A} or AT_{1B} receptors *(42)*. The AT_2R is expressed in the glomerular epithelial cells, proximal tubules, collecting ducts, and parts of the renal vasculature of the adult rat *(43)*. In contrast to the AT_1R, the 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 *(44–46)*. In addition, the AT_2R promotes renal sodium excretion and inhibits proliferation in mesangial cells *(44,47,48)*. Thus, the AT_2R generally appears to 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 is a homologue of ACE that is abundantly expressed in the kidney and acts to counterbalance ACE activity by promoting Ang II degradation to the vasodilator peptide Ang-(1–7) *(49,50)*. Ang-(1–7) acts via the GPCR Mas encoded by the *Mas* protooncogene and counteracts Ang II–AT1R-mediated effects *(51,52)*. 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 reduction of BP following genetic overexpression of ACE2 in their vasculature *(53,54)*. Although ACE2-null mice are normotensive and have normal cardiac structure and function, they exhibit enhanced susceptibility to Ang II-induced hypertension *(55)*. Moreover, Mas-deficient mice exhibit increased blood pressure, endothelial dysfunction, and an imbalance between NO and reactive oxygen species *(56)*. 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) *(57)*.

DEVELOPMENTAL ASPECTS OF THE RAS

The developing metanephric kidney expresses all the components of the RAS (Table 1). The activity of the renal RAS is high during fetal and neonatal life and declines during postnatal maturation *(58,59)*. Immunoreactive Ang II levels are higher in the fetal and newborn than in adult rat kidney *(59)*. The ontogeny of AT_1R and AT_2R mRNA in the kidney differs—AT_2R is expressed earlier than AT_1R, peaks during fetal metanephrogenesis, and rapidly declines postnatally *(60,61)*. AT_1R mRNA expression increases during gestation, peaks perinatally, and declines gradually thereafter *(60–62)*. ACE mRNA and enzymatic activity are expressed in the developing rat kidney, where they are subject to regulation by endogenous Ang II and bradykinin *(59,62)*. In addition, the developing kidney expresses considerable ACE-independent Ang II-generating activity *(63)*, which may compensate for the low ACE levels in the early metanephros *(59)*. The role of the ACE2–Ang-(1–7)–Mas axis and the (pro)renin receptor 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 *(64)*. Premature infants exhibit markedly elevated PRA levels, a finding that is inversely related to postconceptual age *(65)*. In healthy children, plasma renin activity (PRA) is high during the newborn period and declines gradually toward adulthood *(66)*.

Pharmacologic or genetic interruption of the RAS during development alters BP phenotype and causes a spectrum of congenital abnormalities of the kidney and urinary tract (CAKUT) in rodents and renal tubular dysgenesis (RTD) in humans (Table 2) *(67,68)*.

Table 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				*(155)*
			Rat: UB, SM	UB, SM, PT	PT	*(156)*
Renin	Mouse: precursor cells present M of entire kidney M, close to V and G V, G					*(157)*
			Rat: V	V	V	*(58)*
ACE				Rat: PT, G, CD		*(158)*
AT_1	Mouse: UB, M	UB, G	UB, V	PT, UB, SM, G	PT, DT	*(155)*
						(62)
			Rat: G, UB, SM	SM	PT, CD, G	*(60)*
AT_2	Mouse: MM	MM SM		Medullary SM,under renal capsule		*(62)*
		Rat: MM		Condensed M	Medulla, G, V	*(60)*

AGT, angiotensinogen; ACE, angiotensin-converting enzyme; AT_1/AT_2, angiotensin II receptors; UB, ureteric bud; M, mesenchyme; SM, stromal mesenchyme; PT, proximal tubule; G, glomeruli; V, renal vessels; CD, collecting duct.

Adapted from *(159)*, with permission from Springer.

Table 2
Renal and Blood Pressure Phenotypic Effects of Genetic Inactivation of the Renin–Angiotensin System Genes in Mice

Gene	*Gene Function of gene*	*Renal phenotype*	*Blood pressure*	*References*
AGT	Renin substrate	Vascular thickening	Very low	*(160)*
		Interstitial fibrosis		*(161)*
		Delayed glomerular maturation		*(162)*
		Hypoplastic papilla		
		Hydronephrosis		
		Reduced ability to concentrate urine		
Renin	Enzyme that generates ANG I from AGT	Arterial wall thickening	Very low	*(163)*
		Interstitial fibrosis		
		Glomerulosclerosis		
		Hypoplastic papilla		
		Hydronephrosis		
ACE	Enzyme which generates ANG II from ANG I	Arterial wall thickening	Very low	*(164)*
		Hypoplastic papilla and medulla		
		Hydronephrosis		
		Reduced ability to concentrate urine		
$AT_{1A/B}$	Ang II receptor	Decreased kidney weight	Very low	*(165)*
		Delayed glomerular maturation		*(166)*
		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	*(167)*
AT_2	Ang II receptor	Duplicated ureters	High	*(168)*
		Hydronephrosis		*(169)*

Therefore, RAS inhibitors should not be used during pregnancy and should not be used postnatally until nephrogenesis is completed. Beyond these periods of life, high activity of the RAS coupled with persistent expression of the renal AT_1R provide the foundation for the use of the classical RAS inhibitors (ACE inhibitors and AT_1R antagonists) in the

treatment of children with RAS-dependent hypertension (e.g., renovascular hypertension). In addition, both ACE inhibitors and angiotensin receptor blockers may be beneficial in children with primary hypertension, particularly in obese adolescents, who exhibit elevated plasma renin activity *(69)*. Recent availability of aliskiren, the first direct inhibitor of (pro)renin receptor, offers new possibilities in antihypertensive therapy in children that remain to be explored.

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, CYP 11B2 (aldosterone synthase) in the zona glomerulosa of the adrenal glands *(36)*. Aldosterone stimulates reabsorption of Na^+ and secretion of potassium by principal cells in the collecting duct. In turn, the 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) *(70–72)*. Aldosterone-dependent Na^+ reabsorption is due to upregulation of epithelial Na^+ channel-α (alfa) (ENaCα) 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 *(73)*. 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 *(74)*. In addition, aldosterone-induced Sgk1 phosphorylates Ser435 of Af9, causing disruption of the protein–protein interactions of Dot1a, a histone H3 lysine 79 (H3K79) methyltransferase, and Af9. This results in hypomethylation of histone H3 Lys79 and release of transcriptional repression of the ENaCα (alfa) gene. The important role of aldosterone in childhood hypertension is underscored by the ability of mineralocorticoid receptor antagonists not only to reduce elevated BP due to hyperaldosteronism (e.g., adrenal hyperplasia) effectively, but also to offer survival benefits in heart failure and augment potential for renal protection in proteinuric chronic kidney disease.

GLUCOCORTICOIDS

Glucocorticoids are vital for normal development and control of hemodynamic homeostasis. Cortisol or dexamethasone infusion increases BP in the fetal sheep *(75,76)*. Dexamethasone increases BP in $Sgk1^{+/+}$ but not in $Sgk1^{-/-}$ mice *(77)*, indicating that hypertensinogenic effects of glucocorticoids on BP are mediated 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 *(78)*, suggesting that increased fetal glucocorticoid exposure may account for higher systolic blood pressure in childhood. However, no differences in BP and cardiovascular function are detected at school age in children treated neonatally with glucocorticoids for chronic lung disease *(79)*. It is possible that the functional consequences of glucocorticoid therapy during neonatal life may manifest only later in life. However, deleterious effects of excess glucocorticoids on childhood BP are apparent, for example, in conditions such as Cushing's syndrome or glucocorticoid-remediable aldosteronism.

KALLIKREIN–KININ SYSTEM

The kallikrein–kinin system (KKS) plays an important role in the regulation of blood pressure. Kinins, including bradykinin (BK), are formed from kininogen by kininogenase tissue kallikrein *(80)* (Fig. 3). Bradykinin is degraded by ACE, which is also called kininase II *(81)*. Kinins act by binding to the bradykinin receptors B1 (B_1R) and B2 (B_2R). The B_1R is activated by Des-Arg^9-BK produced from BK by kininase I, which mediates tissue injury and inflammation *(82)*. The renal and cardiovascular effects of BK are mediated predominantly through the B_2R. During development kininogen is expressed in the ureteric bud and stromal interstitial cells of the E15 metanephros in the rat and, presumably, in other mammals *(83)*. Following completion of nephrogenesis, kininogen is localized in the collecting duct. The main kininogenase, true tissue kallikrein, is encoded by the *KLK1* gene *(84)*. Transcription of *KLK1* gene is regulated by salt and protein intake, insulin, and mineralocorticoids. Expression of the *KLK1* gene within the kidney is suppressed in chronic phase of renovascular hypertension *(83)*.

In the developing rat kidney, kallikrein mRNA and immunoreactivity are present in the connecting tubule *(85)*. In the mature kidney, tissue kallikrein mRNA is expressed in the distal tubule and glomeruli *(86)*. 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 *(87)*. 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 *(88)*. The human B_1R and B_2R genes are located on chromosome 14 and demonstrate 36% genomic sequence homology *(89)*. Both B_1R and B_2R are members of the seven-transmembrane GPCR family. During metanephrogenesis, B_2R is expressed in both luminal and basolateral aspects of collecting ducts, suggesting that activation of B_2R is important for tubular growth and acquisition of function *(90)*. 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 *(82)*. 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 *(65)*. Stimulation of the B_2R during adult life stimulates production of nitric oxide and prostaglandins resulting in vasodilation and natriuresis *(91)*. 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 *(92)*. Moreover, B_2R-null mice are prone to early onset of salt-sensitive hypertension *(93)*. Interestingly, B_1R receptor blockade in B_2R-null mice produces a significant hypertensive response *(94)*, 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 are associated with hypertension in African-Americans, indicating that the two receptors play a role in BP homeostasis in humans *(95)*. 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 *(96)*.

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 *(97)*. In adult species, AVP supports arterial BP when both the sympathetic system and the RAS are impaired by sympathetic blockade *(98)*. Treatment with a V_1R antagonist has no effect on arterial BP in fetal sheep *(99,100)*. In contrast, antagonism of V_1R during hypotensive hemorrhage impairs the ability of the fetus to maintain BP *(101)*. 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 vasculatures. 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 *(102)*. The major source of NO production in the rat kidney is the renal medulla where NO regulates medullary blood flow, natriuresis, and dieresis *(103,104)*. NO promotes pressure natriuresis via cGMP *(105)*. The effects of Ang II or AVP on medullary blood flow are buffered by the increased production of NO *(103)*, 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 compared with those without a family history of hypertension *(106)*, 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 *(107)*. In fetal rat kidneys, endothelial NO synthase (eNOS) immunoreactivity is first detected in the endothelial cells of the intrarenal capillaries on E14 *(108)*. These findings suggest that eNOS may play a role in regulating renal hemodynamics during fetal life. Moreover, eNOS-knockout mice exhibit abnormal aortic valves, congenital atrial defects, and ventricular septal defects, indicating that eNOS-derived NO plays an important role in the development of the circulatory system *(109)*. The effect of intrarenal infusion of NO antagonist L-NAME on decreases in RBF and GFR is more pronounced in the newborn than adult kidney *(110)*. These effects of NO may act to oppose high RAS activity present in the developing kidney.

Asymmetrical Dimethylarginine

Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of eNOS *(111)*. Infusion of ADMA increases BP and renal vascular resistance, and decreases renal plasma flow during adulthood *(112)*. ADMA levels in fetal umbilical venous plasma are higher than in maternal plasma *(113)*. However, low resistance to umbilical blood flow is maintained despite substantially higher fetal ADMA levels. It is therefore conceivable that NO is a key modulator of fetal vascular tone. Hypertensive children have higher plasma ADMA levels compared with normotensive subjects *(114)*. In contrast, plasma ADMA levels do not differ between normotensive and hypertensive young adults *(115)*. Moreover, plasma ADMA

correlate negatively with vascular resistance *(115)*, suggesting that in a physiological setting ADMA levels in subjects with elevated vascular tone may be lowered to compensate for inappropriately high resistance.

Endothelins

Endothelins (ETs) are vasoconstrictor peptides produced by endothelial cells *(116,117)*. Three ETs were 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 *(118,119)*. ET receptors are located in podocytes, glomeruli, afferent and efferent arterioles, proximal tubules, medullary thick ascending limbs, and collecting ducts *(120)*. The ET_B receptor activation causes natriuresis and vasodilation via release of NO and PGE_2, whereas renal vasoconstriction is mediated by the ET_A receptor *(121)*. In the fetal lamb, the ET_A and ET_B receptors expressed on vascular smooth muscle cells mediate vasoconstriction, whereas ET_B receptors located on endothelial cells mediate vasodilation *(122,123)*. In the renal circulation of fetal sheep, ET-1, acting via the ET_B receptor, causes vasodilation *(124)*. However, ET_A receptor-mediated vasoconstriction also contributes to the regulation of the fetal renal vascular tone *(125)*. 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 genetic inactivation of either ET-1 or both ET_A and ET_B receptors *(126,127)*. Moreover, BP increases further with high salt intake, indicating that combined ET_A /ET_B receptor deficiency causes 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) *(128–131)*. Natriuretic peptides act by binding to three guanylyl cyclase-linked receptors: NPR-A, NPR-B, and NPR-C *(132)*. 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 *(132,133)*, and are rapidly degraded in the lung and kidney by neutral endopeptidase *(134)*. ANP and BNP reduce 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 *(135)*. ANP and BNP peptide levels are higher in fetal than adult ventricles, indicating that the relative contribution of ventricular ANP is greater during embryonic than adult life *(136–138)*. ANP and BNP mRNAs are expressed on E8 in the mouse and increase during gestation, suggesting that both ANP and BNP play a role in the formation of the developing heart. Circulating ANP levels are higher in the fetal than adult rat or sheep *(137,139)*. Infusion of ANP into the circulation of fetal sheep decreases BP and causes diuresis *(140)*. 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, volume loading, hypoxia, or increase in osmolality *(139,141)*. Plasma levels of ANP are higher in preterm than term infants *(142)*. In the full-term infants, circulating ANP levels increase during the first week of life and decrease thereafter *(143)*. 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 required for rapid growth. Although BP remains normal

in BNP-null mice *(144)*, ANP-null mice develop hypertension later in life *(145)*. 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 *(146,147)*.

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 *(147)*. Brain RAS is activated by low protein (LP) diet and hypertensive adult offspring of LP-fed dams have increased pressor response to Ang II *(148,149)*. Thus, inappropriate activation of the RAS may link fetal life to childhood and adult hypertension. Interestingly, LP maternal diet has been reported to result in decreased methylation of the promoter region of $AT_{1B}R$ in the offspring *(150)*. It is conceivable that epigenetic modifications of the $AT_{1B}R$ gene may represent one of the mechanisms implicated in developmental programming of hypertension by an aberrant RAS. LP diet or caloric restriction during gestation causes a decrease in the renal kallikrein activity, blunted vasorelaxation to NO infusion, an increase in vascular superoxide anion concentration, and a decrease in superoxide dismutase activity in offspring of dams with such restricted diets *(151–153)*. In addition, heterozygous eNOS offspring born to eNOS-null mothers exhibit impaired endothelium-dependent vasodilation compared to heterozygous pups born to $eNOS^{+/+}$ mothers *(154)*. These observations indicate that impairment in endothelium-dependent vascular function is associated with developmentally programmed hypertension and that the eNOS maternal genotype modulates a genetic predisposition to hypertension. Further studies are needed to establish the mechanisms by which alterations in the antenatal environment impact vasoactive factor systems and their interplay to program hypertension during postnatal life.

SUMMARY

Many vasoactive substances regulate cardiovascular homeostasis during development, and more are discovered each year. Many cardiovascular factors exert pleiotropic actions both systemically and within diverse organ systems. Continued discovery of new vasoactive substances and more complete knowledge of their role during development will increase our understanding of the developmental origin of hypertension and cardiovascular disease and should help in the development of strategies that will minimize the impact of these substances on hypertension Further work is needed to define more precisely the role of emerging cardiovascular regulatory factors and to understand their growing relevance to a number of conditions in animal models of human disease and in human diseases including hypertension.

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3 Cardiovascular and Autonomic Influences on Blood Pressure

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Contents

The cardiovascular system provides appropriate organ and tissue perfusion at rest and at times of stress by regulation of blood pressure. The arterial pressure level reflects the composite activities of the heart and the peripheral circulation.

CONTROL OF BLOOD PRESSURE

Although the relationship between pressure and flow through the vascular tree is not linear, blood pressure can be expressed as the product of cardiac output (CO) and peripheral resistance *(1)* (Table 1). These variables are closely intertwined, and the control

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_3
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Table 1
Factors Influencing Arterial Pressure as the Product of Cardiac Output and Peripheral Resistance

Cardiac output
Heart rate
Stroke volume
Venous return
Myocardial contractility
Blood volume
Peripheral resistance
Adrenergic nerves
Circulating catecholamines
Other vasoactive substances
Acetylcholine
Angiotensin II (angiotensin 1–7, angiotensin 2–8)
Calcitonin gene-related peptide (intermedin, adrenomedullin 2)
Carbon monoxide
Endothelium-derived contracting factor
Hydrogen sulfide
Kinins
Neuropeptides (neurotensin, NPY, substance P)
Nitric oxide
Oxytocin
Prostanoids (prostaglandins, HETEs, leukotrienes, thromboxanes)
Serotonin
Substance P
Vasopressin
Ions and cellular regulations (e.g., calcium, sodium, chloride, potassium, magnesium, manganese, and trace metals, pH)
Hematocrit (viscosity)
Reactive oxygen species

mechanisms for pressure regulation involve more than simply a direct change in either CO or peripheral resistance *(2)*. The major determinant of blood pressure at rest is arteriolar resistance; during exercise, CO assumes a more important role.

Cardiac Output

CO is defined as the volume of blood pumped by the left ventricle of the heart into the aorta and thence to the circulation. In general CO is expressed in liters/minute. It represents the circulatory status of the organism and plays a critical role in maintenance of blood pressure in health and disease. Blood pressure is determined by the product of CO and systemic vascular resistance.

CO varies widely depending on metabolic and physical activity, age, and size of the body. In healthy young males, resting cardiac output is 5.6 L/min and is about 20% lower in females. As this value varies consistently with the body surface area (BSA), it is also expressed as cardiac index, which is the cardiac output per square meter BSA. This value is about 3 L/min/m *(2)*. Babies have a higher cardiac index at 5.5 L/min/m^2 which is even higher in preterm babies.

CO is tightly regulated to meet the body's rapidly changing metabolic needs. Primary and secondary mechanisms govern CO: primary mechanisms operate quickly for acute regulation, and secondary mechanisms have a slower onset and regulate long-term aspects of cardiac function. CO is derived from the product of stroke volume (volume represented by the volume of blood pumped by the heart in one beat) and the heart rate (HR) per minute. In infancy and early childhood, CO is increased mainly by an increase in HR because the capacity of the cardiac muscle to increase stroke volume during this period is limited.

Stroke Volume

Stroke volume depends on three primary factors, all of which are interrelated and not mutually exclusive.

1. *Preload* reflects venous filling of the right ventricle which subsequently determines the volume of blood available to be pumped to the circulation by the left ventricle. Preload is classically compromised in dehydration and hemorrhage.
2. *Afterload* is caused by peripheral arterial resistance and intrinsic ventricular wall stress. Afterload determines diastolic pressure and thus has a significant impact on mean arterial pressure and resulting tissue perfusion. Afterload is decreased due to vasoplegia in septic shock and increased due to vasoconstriction in hypothermia.
3. *Myocardial contractility* reflects the inherent capacity of the cardiac muscle to pump blood. This function is compromised in myocarditis and some forms of cardiomyopathy. These primary factors could be altered by secondary factors in response to the physiological state of the individual.

PRELOAD

CO output is determined primarily by the volume of venous blood that fills the ventricle during diastole, the preload or end-diastolic volume. The adult heart can pump up to 15 L of blood per minute, although the usual resting CO is only 5.6 L/min. The Frank–Starling law describes the inherent ability of the heart to regulate its output in the face of a rapidly changing preload. Increasing preload increases the end-diastolic volume which results in the stretch of the muscle fibers. Hence, increased volume at the end of diastole leads to increased stroke volume by an immediate, increased, and effective ejection during systole. This ensures that even when end-diastolic volume or filling is increased, the end-systolic volume or the volume of blood left in the ventricle at the end of systole does not increase, as all of the extra volume is pumped out. However, this process does not continue indefinitely. The energy output of a heart muscle fiber increases with increasing fiber length up to a point, beyond which further extension of the fiber results in a decrease in its contractile force, causing a reduction in stroke volume. An important aspect of the Frank–Starling law is that a change in the afterload (or outflow resistance) has almost no influence on cardiac output. Preload-dependent regulation of stroke volume is also called *heterometric regulation*. Stretching of the ventricle stretches the sinus node in the wall of the right atrium,

which increases its rate of firing and increases the heart rate by 10–15%. The stretched right atrium also initiates a reflex called the Bainbridge reflex which increases heart rate in euvolemic states. In summary, increasing preload increases stroke volume and heart rate, and thus preload is a major player in enhancing cardiac output.

AFTERLOAD

Afterload is the force that opposes or resists ventricular emptying. After the ventricle has ejected its contents, the resulting increase in aortic pressure closes the aortic valve and maintains a back pressure that the next cycle of systole has to overcome. Components of the aortic back pressure include the tension developed in the aortic walls, peripheral vascular resistance, the reflected pressure waves within the ventricle, and its distribution throughout the ventricular wall. Thus ventricular pressure, myocardial thickness, and peripheral resistance all contribute to systolic wall stress, which together determine afterload. Mean arterial pressure (calculated as 2 × diastolic plus 1 × systolic BP divided by 3), which is related to CO and peripheral resistance, serves as an indication of afterload. Mean afterload is normally kept constant by central cardiovascular and autonomic control.

Because the afterload does not allow the ventricle to empty completely, a percentage of the original venous return remains in the heart. The term *ejection fraction* (EF) describes the amount of blood ejected from the ventricle during one systolic wave (stroke volume, SV) divided by the amount of blood in the ventricle at the end of diastole (left ventricular end-diastolic volume, LVEDV).

$$EF = SV/LVEDV$$

This is quantified with echocardiography by measuring the shortening fraction (SF) which is given by measuring the diameters, rather than volumes, of the left ventricle during systole and at the end of diastole, i.e., SF = LV end-diastolic diameter − LV end-systolic diameter, LV end-diastolic diameter of the muscle fiber, which correlates directly with contractility. Typically the EF for a normal adult is 0.50–0.75, while the EF is 0.18–0.42, with levels >0.3 being considered "normal" and EF of 0.26–0.30 considered to be indicative of a mild decrease in contractile function. A decrease in SF generally precedes a detectable decrease in EF. While left and right ventricular diastolic volumes do increase with gestational and postnatal age *(3)*, the EF remains the same.

MYOCARDIAL CONTRACTILITY

Myocardial contractility accounts for the increases in contractile force of a muscle fiber without an accompanying change in fiber length. This property of cardiac muscle is called *homeotropic regulation*. The heart is richly supplied with autonomic nerves, both sympathetic and parasympathetic, that have profound effects on heart rate and contractility. The resting normal sympathetic tone maintains cardiac contractility at 20% greater than that in the denervated heart. Increased sympathetic input to the heart can significantly increase both heart rate and contractile force, up to 100%. Parasympathetic innervation, on the other hand, reduces heart rate and contractile force through nerve fibers predominantly supplying the atria. In addition, intracardiac parasympathetic ganglia exert selective inhibitory effects on left ventricular contractility *(4)*. However, contractility can only be decreased by about 20%. Parasympathetic effects are mediated by the release of acetylcholine activity.

Table 2
Some Drugs Showing Selectivity for Adrenergic and Dopamine Receptor Subtypes *(19)*

Drug name	*Agonists*	*Antagonists*
Nonselective	Norepinephrine	Phentolamine
α_1	Methoxamine	Prazosin
α_{1A}	NS-49 A-61603	(+) Niguldipine, 5-methyl urapidil, KMD-3213
α_{1B}		
α_{1D}	Naftopidil	BMY-7378
α_2	14304	Idazoxan Rauwolscine Yohimbine
$\alpha_{2A/D}$		BRL 48962
α_{2B}		BRL 41992
α_{2C}		WB 4101
β-Adrenoceptor		
Nonselective	Isoproterenol	Propranolol Pindolol
β_1	Prenalterol (-) Ro-363	Metoprolol Atenolol ICI 89,406 CGP20712A
β_2	Salbutamol Terbutaline Zinterol	Butoxamine ICI 118,551 (inverse agonist)
β_3	BRL 37344 CL 316243	SR-59230 (not blocked by propranolol)
Dopamine receptor		
Nonselective	Dopamine	
D_1-like	Fenoldopam[a]	SCH 23390[a]
D_1	A 68930	
D_5	SKF 82958	4-Chloro-3-hydroxy-7-methyl-5,6,7,8,9,14-hexahydro-dibenz[d,g]azecine
D_2-like	LY 171555 SKF103376	YM 09151 Domperidone
D_2	U91356A U95666	L741,626
D_3	PD128907 7-hydroxyPIPAT	Nafadotride U-99,194A
D_4	PD168077	U-101958

[a]Selective for D_1-like receptors but cannot distinguish between D_1 and D_5 receptors.

Only muscarinic m2 receptors have been thought to be expressed in the heart. However, m1 and m3 muscarinic receptors may also be present in cardiac myocytes *(5)*. Sympathetic enhancement of cardiac contractility is mediated by norepinephrine from the cardiac sympathetic nerves. Norepinephrine causes an increase in shortening of the muscle fiber with a constant preload and total load resulting in increased stroke volume. This effect is mediated by the stimulation of β-adrenergic receptors, mainly of the β_1 subtype (see Table 2) on the cardiac membranes leading to an increase in cyclic AMP. cAMP increases phosphorylase B activity, which stimulates glycogen metabolism, and increases the energy needed for enhanced contractility. The combined effects of sympathetic stimulation on HR and contractility can cause a two- to threefold increase in cardiac output. Neurotrophins, including nerve growth factor, are important in cardiac sympathetic innervation, acting through the tropomyosin-related tyrosine kinase receptor to a greater extent than p75 receptor *(6)*. Neurturin, a member of the glial-cell-derived neurotrophic factor, is important in the development of cardiac parasympathetic neurons *(7)*.

Calcium is necessary for effective contraction of cardiac muscle. Action potential causes release of calcium into the sarcoplasm of the muscle. Instantaneously, calcium ions diffuse into the myofibrils and catalyze the chemical reactions that promote sliding of actin and myosin filaments along one another, producing muscle contraction. Because muscle sarcoplasm does not have a large store of calcium, large amounts of extracellular calcium are needed to diffuse into the T-tubules, where they are bound to glycoproteins, and released as needed to enhance contractility. In atrial cells that do not have T-tubules, calcium release may be limited to peripheral junctions on the cell surface but calcium may also arise from sarcoplasmic reticulum and the mitochondria *(8)*. In the adult heart, excitation–contraction coupling caused by calcium-induced calcium release (CICR) is mediated by L-type Ca^{2+} channels while this is mediated by the reverse-mode Na^{+}–Ca^{2+} exchanger (NCX) activity in the developing heart *(9)*.

HEART RATE AND RHYTHM

Factors affecting heart rate do so by altering the electric properties of the cardiac pacemaker cells, which have an intrinsic rate that is age dependent, being higher in infancy and decreasing with age. The autonomic nervous system exerts the most profound influence on heart rate. The sympathetic and parasympathetic systems act by changing the rate of spontaneous depolarization of the resting potential in the cardiac pacemaker cells. While sympathetic stimulation causes an increase in heart rate, parasympathetic stimulation causes a decrease in heart rate. These reflexes are immediate and represent critical survival mechanisms. During periods of tachycardia, peak ejection velocity is increased. The net effect of the tachycardia is an increased cardiac output. However, outside the normal physiologic range, large increases or decreases in heart rate result in a decrease in the net cardiac output. For example, in the adult, tachycardia of 170 beats/min or greater allows too little time for ventricular filling, and therefore stroke volume. The decreased stroke volume may not be overcome by the increased heart rate. Lower than normal heart rate, or bradycardia, causes a decreased cardiac output because stroke volume does not increase sufficiently to meet the requirements of the individual to sustain CO. At heart rates below 40 beats/min (in the adult), the increase in preload due to increased filling time is limited because major ventricular filling, which occurs early in diastole, is not maintained throughout the extent of the diastolic period.

Heart rate is one of the most important determinants of myocardial energy consumption. Generally it is more energy efficient to increase cardiac output by increasing stroke volume, rather than by increasing heart rate. Infants and children are more likely to increase their heart rate and thus expend more energy in increasing their cardiac output during stress.

PRIMARY REGULATION OF CARDIAC OUTPUT DURING DEVELOPMENT

Effective circulation is necessary in very early embryonic development and parallels structural development of the heart *(10)*. As early as 5 weeks postconception in humans, the basic circulatory parameter, heart rate, is present at about 100 beats/min. Recent advances have elucidated the genetic control of embryonic differentiation of cardiac pacemaker cells and have implicated genes in the establishment of heart rate. Shox2 homeodomain transcription factor is essential for the development of the sinoatrial node and pacemaker by repressing Nkx2-5 *(11)*.

CO is very dependent on heart rate and, after formation of the four-chambered heart, on atrioventricular synchrony. Systolic function of the heart and, consequently, CO increases with gestational age. The ejection fraction of the embryonic ventricle is roughly 30–50%, similar to adults. The fetal heart, however, has a limited ability to increase work following stretch, so the Frank–Starling curve is limited compared to adults. The lower wall stress in the embryo, due to a smaller ventricular size and lower pressures, reduces the total afterload and enhances cardiac output in the face of a high peripheral resistance. Afterload due to wall stress increases as gestation progresses, reflecting the increase in ventricular size and transmural pressures even while peripheral vascular resistance decreases.

SECONDARY REGULATION OF CARDIAC OUTPUT

A variety of factors operate in the normal individual to regulate CO over the long term. These secondary control mechanisms do not have as great an influence on the heart as the components previously described. Secondary controls include cardiovascular reflexes and hormonal influences. Cardiopulmonary receptors, which are sensory nerve endings in the atria, ventricles, coronary vessels, and lungs, have chemo- and mechanosensitive properties. The activity of these receptors is relayed to the nucleus of the tractus solitarius via vagal afferents and spinal sympathetic afferent fibers. Stimulation of these receptors evokes responses similar to those noted with arterial baroreceptors (see below). Thus, an increase in distension of the atria results in a decrease in circulating levels of vasopressin, aldosterone, and renin, among other hormones, but causes an increase in the natriuretic factors synthesized by the atrium and the ventricles (atrial natriuretic peptide, brain natriuretic peptide, C-type natriuretic peptide). Circulating atrial natriuretic peptide levels decrease with gestational and postnatal age *(12)*. Depressor reflexes in the heart originating mainly from the inferoposterior wall of the left ventricle promote bradycardia, vasodilatation, and hypotension (Bezold–Jarisch reflex) *(13)*. These are mediated by increased parasympathetic and decreased sympathetic activity. Left ventricular mechanoreceptor stimulation can also attenuate arterial baroreflex control of heart rate. Decreased activity of cardiac vagal afferents results in enhanced sympathetic activity and increased vascular resistance, renin release, and vasopressin secretion. Alterations in extracellular fluid volume influence CO via changes in preload and blood pressure. In fetal and newborn animals

cardiopulmonary receptors have minimal influence in the regulation of cardiovascular and autonomic responses to changes in blood pressure or blood volume *(14)*.

Peripheral Resistance

Blood flow through a vessel is determined by two primary factors: the amount of pressure forcing the blood through the vessel and the resistance to flow. The resistance to flow in a blood vessel is best described as impedance because this takes into account inertial properties and viscosity of blood elastic properties of blood vessels and the variable geometries of blood vessels during phasic flow. One of the most important factors influencing the flow through the arteries is the vessel diameter, since the conductance is proportional to the fourth power of the diameter. Therefore, flow is influenced more by changes in vascular resistance than by pressure changes. The different variables influencing peripheral resistance are listed in Table 1.

CONTROL MECHANISMS FOR BLOOD PRESSURE REGULATION

The short-term adjustment and long-term control of blood pressure are supplied by a hierarchy of pressure controls *(2)*. The cardiovascular reflexes are the most rapidly acting pressure control mechanisms. They are activated within seconds, and the effects may last from a few minutes to a few days. The pressure controls acting with intermediate rapidity include capillary fluid shifts, stress relaxation, and hormonal control that include the angiotensin and vasopressin systems. These systems, like the cardiovascular reflexes, function to buffer acute changes in pressure. Long-term control is afforded by long-term regulation of body fluids *(2)*.

ARTERIAL BARORECEPTORS

The degree of arteriolar constriction is determined by a balance between tonic output from the pressor areas of the cardiovascular center and the degree of inhibition from the baroreceptors. The arterial baroreceptors are the major fast reacting, slowly adapting feedback elements to the central neural cardiovascular regulatory system and operate to limit sudden changes in blood pressure. Their mechanosensitive nerve endings are located at the medial–adventitial border of blood vessels with elastic structure, mainly at the aortic arch and carotid sinuses. The receptors respond to deformation of the vessel in any direction, i.e., circumferential and longitudinal stretch. This results in the stimulation of mechanosensitive channels that contain degenerin/epithelial sodium channel (DEG/ENaC) *(15,16)*. The pressure–diameter relationship is concave with the greatest distensibility at about 120–140 mmHg. There are two types of receptors in the carotid sinus: type I receptors are thin myelinated fibers and type II receptors are thick myelinated fibers with fine end branches terminating in neurofibrillar end plates. The latter receptors are also seen in the aortic arch. Postnatal hypoxemia is associated with an increased sensitivity of peripheral chemoreceptors that may be related to increased expression and activity of angiotensin type 1 receptors *(17)*.

An increase in blood pressure stimulates the mechanosensitive receptors in the baroreceptors and causes inhibition of the sympathetic nervous system and activation of the parasympathetic nervous system. This results in a decrease in heart rate, myocardial contractility, peripheral vascular resistance, and venous return. A decrease in blood pressure

decreases mechanosensitive stimulation of the baroreceptors and causes inhibition of the parasympathetic nervous system and the activation of the sympathetic nervous system. This results in an increase in heart rate, myocardial contractility, peripheral vascular resistance, and venous return *(18)*. Changes in osmotic pressure affect other homeostatic mechanisms such as thirst and vasopressin release by the activation of ion channels *(19)*. Shear stress resulting from increased blood pressure also sets into motion the generation of endogenous vasodilators such as nitric oxide which cause vasodilatation to oppose the increase in blood pressure.

Sensory innervation of the aortic arch is derived from the vagus while the carotid sinus nerve originates from the glossopharyngeal nerve. The majority of the afferent nerves are myelinated type A fibers. These fibers have large and intermediate spikes of 40–120 μV corresponding to the high distensibility region. At normal pressure levels, these fibers transmit mainly the dynamic components of blood pressure, pulse pressure (dp/dt), and pulse frequency. The receptor sensitivity is highest at the lower end (60–100 mmHg) of the high distensibility region of the blood vessel. There are a few nonmyelinated type C fibers, located mainly in the carotid sinus nerve. The spikes are small (5–10 μV), have a higher static threshold (120–150 mmHg), correspond to the low distensibility region, and mainly transmit mean pressure. The type C fibers can be activated independently by sympathetic stimuli.

The arterial baroreceptors are more effective in compensating for a fall rather than a rise in mean arterial pressure. The interaction between mean and pulsatile components can be of considerable importance in the hemodynamic response to hemorrhage. For example, the initial response to moderate hemorrhage results in a decrease in pulse pressure with maintenance of mean arterial pressure. Decreasing pulse pressure results in a redistribution of CO to the mesenteric and cardiac circulations with no effect on the renal circulation.

Information carried by the afferent limb of the reflex arc from the baroreceptors is relayed to the lower brain stem via the vagus and glossopharyngeal nerves. Most secondary neurons are located at the nucleus of the tractus solitarius, and projections are directed to various regions of the brain stem. The effectors of the baroreceptors include systems that have an immediate but short-term effect on circulatory function and those that have delayed but long-term effects. Examples of the former are resistance vessels—arterioles throughout the systemic circulation—the capacitance vessels—veins and arteries—and the heart. An example of a system with a long-term effect is the kidney. In addition, neural reflexes may influence circulating levels of several hormones (e.g., renin, vasopressin) with short- and long-term effects on cardiovascular regulation. The effect of neural reflexes on the kidneys may be direct, through renal sympathetic nerve activity, or indirect, through circulating catecholamines.

Norepinephrine-containing nerve endings are found in the carotid sinus and aortic arch and may influence the sensitivity of the sinus reflex. Norepinephrine, given intravenously, decreases the distensibility of the sinus at low pressures but increases the distensibility at high pressure. In the conscious dog, sinus hypotension induces a reflex tachycardia and sympathetic vasoconstriction of the skeletal resistance vessels. The changes in the renal and mesenteric beds (45% of total peripheral resistance) seem to be solely due to autoregulation. In the anesthetized dog, sinus hypotension induces a greater magnitude and a more generalized pattern of sympathetic vasoconstriction and may include both resistance and capacitance vessels. Several paracrine factors that affect the sensitivity of arterial baroreceptors have been reported, including prostanoids and nitric oxide. In general, vasoconstrictors decrease baroreceptor sensitivity while vasodilators have the converse effect.

However, nitric oxide decreases baroreceptor sensitivity independent of its vasodilator action. Reactive oxygen species (ROS) also decrease baroreceptor sensitivity, a mechanism that may contribute to the increase in systemic blood pressure caused by ROS *(20)*. Reduction in ROS decreases central sympathetic nerve activity *(21)*.

ADAPTATION OF THE BARORECEPTORS

The baroreceptors exert a tonic inhibitory influence on peripheral sympathetic activity. Baroreceptor nerves interact by mutual inhibitory addition; with a decrease in pressure, there is less reflex inhibition and a resultant increase in sympathetic outflow. While transient baroreceptor-induced changes in heart rate are primarily mediated by the parasympathetic nervous system, steady-state responses are due to a greater involvement of the sympathetic nervous system. A sudden increase in pressure (with resultant stretching of the receptors) causes an immediate increase in baroreceptor firing rate. With continued elevation of the pressure, however, there is a decrease in the rate of baroreceptor firing. Initially the decrease is rapid, and during the succeeding hours and days it slows down. This adaptation, or resetting, in response to a lower or higher pressure seems to be complete in 2 days. This adaptation can occur at the receptor and nervous signal pathway *(2)*. The resetting of the baroreflex is much more rapid in adults than in infants *(22)*.

ARTERIAL BARORECEPTORS DURING DEVELOPMENT

Studies in humans and experimental animals suggest that arterial baroreceptors are present in the fetus and undergo postnatal maturation *(22,23)*. There is an enhanced sensitivity of the efferent limb of the baroreflex in fetal life *(22)*. Neurotrophins are important in cardiac sympathetic innervation *(7)*, and brain-derived neurotrophic factor may mediate the postnatal maturation of the baroreceptor reflex *(24)*. In adults with intact arterial baroreceptors, a rapid head-up tilt is accompanied by an immediate increase in heart rate and peripheral vascular resistance with maintenance of mean arterial pressure in the upper body. Several studies have suggested that in healthy preterm and term human infants, head-up tilting also increases heart rate in proportion to the degree of tilting. However, other studies have shown that in healthy preterm infants with a postconceptional age of 28–32 weeks, a 45° head-up tilt results in an increase in peripheral resistance without any significant changes in heart rate *(14)*. The increase in heart rate with a 45° head-up tilt increases with postconceptional age. In the conscious newborn dog, the magnitude of the increase in mean arterial pressure and peripheral resistance following bilateral carotid occlusion is less than that in the adult. In addition, these changes occur without alterations in heart rate, similar to the effects noted in infants. In fetal sheep, only the increase in heart rate with a decrease in blood pressure is noted. There is no relationship of arterial pressure and heart rate variability immediately after birth, but the fetal pattern resumes a few hours later *(25)*. Recent research has suggested that the prone sleeping position impairs the development of cardiovascular reflexes, even in term infants, especially during the 2- to 3-month age group when sudden infant death syndrome (SIDS) is most prevalent *(26,27)*.

Newborn lambs exhibit the classic inverse relationship between heart rate and blood pressure, but the sensitivity is only about 50% that of the adult. The responses to small changes in blood pressure are similar in fetal and newborn lambs. However, when the change in blood pressure is greater than 15% the responses are different. In newborn lambs a progressive tachycardia accompanies the increasing hypotension, due to a combination

of increased sympathetic outflow and parasympathetic withdrawal. There is no progressive tachycardia in the fetus; in fact, when the blood pressure change is greater than 50%, bradycardia occurs, apparently due to augmentation of vagal parasympathetic tone.

There are age-dependent differences in the ability of the piglet to compensate for hemorrhage and hypoxia *(28)*. Neonatal swine are able to compensate with greater facility for venous than arterial hemorrhage *(29)*. Volume expansion inhibits the sympathetic nervous system to a greater extent in older than in newborn lambs. Increasing arterial pressure by intravenous administration of vasoconstrictor agents results in smaller changes in heart rate in the newborn animal as well. Completion of sympathetic efferent pathways occurs before baroreceptor reflex activity is capable of modulating cardiac sympathetic activity. Thus, maturation of baroreceptor reflex activity may be dependent on development of baroreceptor function or of connections between baroreceptor and sympathetic efferents *(22)*. The changes in baroreflexes during development are thought to be caused by afferent, central integration, and efferent pathways. The maturation of receptors for various humoral and hormonal agents (e.g., angiotensin II, glucocorticoids, prostanoids, vasopressin) has been shown to affect baroreflex function.

Autonomic Regulation of Blood Pressure

Regulation of the distribution of CO and maintenance of blood pressure are major functions of the autonomic nervous system. The arterioles are normally in a continuous state of partial constriction, largely determined by an equilibrium between vasoconstrictor influences from the cardiovascular centers and the inhibitory input from the peripheral baroreceptors. The veins also receive autonomic innervation. Adrenergic nerves induce venous constriction with a resultant decrease in capacitance which increases venous return and CO. The effects of the adrenergic nervous system are conveyed by the neurotransmitters: norepinephrine, epinephrine, and dopamine.

Catecholamines. Epinephrine is released mainly from the adrenal medulla, while norepinephrine is released mainly in terminal nerve endings. In organs with dopaminergic nerves, a greater proportion of catecholamine released is dopamine. Norepinephrine synthesized at peripheral nerve endings is stored in subcellular granules. After a specific stimulus, it is released into the synaptic cleft where it interacts with specific receptors at the effector cell. The neurotransmitter is inactivated to a large extent by reuptake into the storage granules. This reuptake process (reuptake-1) is stereoselective, sodium dependent, and of high affinity. A presynaptic reuptake that is of low affinity and nonsodium dependent has been termed reuptake-2. There are specific amine transporters. Although the enzymatic degradation of the neurotransmitter by monoamine oxidase and catechol-*O*-methyltransferase is much less important in termination of neurotransmitter action in nervous tissue, in vascular smooth muscles this metabolism plays an important role *(30)*. More recently a third monoamine oxidase (MAOC or renalase) has been reported to degrade circulating catecholamines, especially dopamine *(31)*. The remainder of the neurotransmitter which escapes reuptake-1 and -2 is released into the circulation. Since only about 20% of the total appears in the circulating pool the plasma levels of catecholamines are merely a rough index of adrenergic activity.

Adrenergic and dopaminergic receptors. For the neurotransmitter to exert its specific effect, it must occupy a specific receptor on the cell surface. Catecholamines can occupy specific pre- and postsynaptic receptors. Each receptor has different subtypes *(32–35)*. Table 2 lists some drugs that have relative selectivity to each particular receptor

subtype in the peripheral vascular bed. Occupation of presynaptic α_2-adrenergic and dopamine receptors inhibits norepinephrine release. Occupation of presynaptic β-receptors enhances norepinephrine release. At low levels of nerve stimulation, norepinephrine release is increased; at high levels of stimulation, the inhibitory effects of presynaptic α_2-adrenergic receptors predominate, acting as a short-loop feedback. The antihypertensive effects of dopamine agonists and (β-adrenergic antagonists) may be due in part to their ability to decrease release of norepinephrine at the terminal nerve endings.

α_1-Adrenergic receptors. Three α_1-adrenergic receptors are expressed in mammals, α_{1A} (originally designated as the α_{1C} when cloned), α_{1B}, and α_{1D}. The effects in the vascular bed are receptor subtype specific. Thus, α_{1A} may mediate contraction of renal and caudal arteries, whereas α_{1D}-adrenergic receptors may regulate the contraction of the aorta, femoral, iliac, and superior mesenteric arteries. Mice deficient of the α_{1A}-adrenergic receptor have decreased blood pressure as do mice deficient of the α_{1D}-adrenergic receptor *(35)*. The α_{1D} receptor-deficient mice are resistant to the hypertensive effect of sodium chloride. In contrast, α_{1B}-adrenergic receptors may not regulate vascular smooth muscle contraction. Mice deficient of the α_{1B}-adrenergic receptor have normal blood pressure in the basal state *(36,37)*. Neonatal cardiac myocytes hypertrophy is mediated primarily by the α_{1A}- and α_{1B}-adrenergic receptors. Aortic hypertrophy, on the other hand, is primarily due to the actions of the α_{1D}-adrenergic receptors.

α_2-Adrenergic receptors. There are three α_2-adrenergic receptor subtypes, $\alpha_{2A/D}$, α_{2B}, and α_{2C}. The α_{2A} class predominates and mediates most of the classical effects of α_2-adrenergic stimulation, to decrease blood pressure and heart rate, induce sedation, and consolidate working memory. In contrast, α_{2B}-adrenergic receptors, predominantly found outside of the central nervous system at extrajunctional or postsynaptic sites, produce vasoconstriction and thus counteract the hypotensive effects of α_{2A}-adrenergic receptor stimulation. α_{2B}-Adrenergic receptors are important in vascularization of the placenta. α_{2C}-Adrenergic receptors do not have cardiovascular effects but may mediate the hypothermic response to β_2-adrenergic stimulation *(38)* and feedback inhibition of adrenal catecholamine release. The effects of the α_2-adrenergic receptors are exerted in both adrenergic (autoreceptors) and nonadrenergic (heteroreceptors) cells *(33)*.

β-Adrenergic receptors. There are three β-adrenergic receptors, β_1, β_2, and β_3. Disruption of either the β_1-, β_2-adrenergic receptor, or both does not affect heart rate or resting blood pressure in mice. Mice lacking the β_1-adrenergic receptor are unresponsive to cardiac β-adrenergic receptor stimulation, suggesting that neither β_2- nor β_3-adrenergic receptors play a role in the inotropic or chronotropic responses in the mouse *(39)*. Indeed, the effect of the non-β-adrenergic subtype receptor agonist isoproterenol is not altered in β_2-adrenergic receptor null mice. However, the hypotensive response to isoproterenol is impaired in both β_1- and β_2-adrenergic null mice *(40,41)*. β_3-Adrenergic receptors do not have major effects on the cardiovascular system *(42)*.

Dopamine receptors. Dopamine is an important regulator of blood pressure. Presynaptic/junctional and postsynaptic/junctional or extrasynaptic dopamine receptors are found in many organs, including the heart *(43–45)* and vascular beds. Dopamine's actions on renal hemodynamics, epithelial transport, and humoral agents such as aldosterone, catecholamines, endothelin, prolactin, pro-opiomelanocortin, renin, and vasopressin place it in a central homeostatic position for the regulation of extracellular fluid volume and blood pressure. Dopamine also modulates fluid and sodium intake via its actions in the central nervous system and gastrointestinal tract and by regulation of cardiovascular centers that control the functions of the heart, arteries, and veins. Abnormalities in dopamine production

and receptor function accompany a high percentage of human essential hypertension and several forms of rodent genetic hypertension. Dopamine receptor genes, as well as genes encoding their regulators, are in loci that have been linked to hypertension in humans and in rodents. Moreover, allelic variants (single nucleotide polymorphisms, SNPs) of genes that encode the regulators of the dopamine receptors, alone or in combination with variants of genes that encode proteins that regulate the renin–angiotensin system, are associated with human essential hypertension.

Dopamine receptors. Each of the five dopamine receptor subtypes (D_1, D_2, D_3, D_4, and D_5) participates in the regulation of blood pressure by mechanisms specific for the subtype *(46–48)*. Both the D_1-like dopamine receptors (D_1 and D_5) and the D_3 receptor decrease epithelial sodium transport *(46,47)*. D_4 receptors inhibit the effects of aldosterone and vasopressin in the renal cortical collecting duct *(48,49)*. D_2-like receptors (e.g., D_2 receptor) under certain circumstances may increase sodium transport *(50,51)*. Dopamine can regulate the secretion and receptors of several humoral agents (e.g., the D_1, D_3, and D_4 receptors interact with the renin–angiotensin system). The D_1-like receptors are vasodilatory, while the D_2-like receptors can mediate vasodilation or vasoconstriction depending upon the starting vascular resistance. When vascular resistance is high, D_2-like receptors are vasodilatory by inhibition of norepinephrine release. However, when vascular resistance is low, D_2-like receptors mediate vasoconstriction probably via the D_3 receptor *(51)*. The D_1 and D_5 receptors have antioxidant functions *(33,50–53)*.

Signal transduction. The signal resulting from occupation of cell membrane receptors is amplified by the intervention of other agents called second messengers. Occupation of either the β-adrenergic receptor subtype or the D_1-like class of dopamine receptor by agonists stimulates adenylyl cyclases; agonist occupancy of β_2-adrenergic receptors or dopamine D_2 receptors leads to inhibition of adenylyl cyclases. The changes in intracellular cyclic adenosine monophosphate levels alter the activities of certain enzymes, e.g., protein kinase A, and mediate the eventual response of the effector cell. Certain compounds (e.g., nitric oxide) exert their vasodilatory effect by stimulation of guanylate cyclase activity *(54)*. Another second messenger is associated with the phosphoinositide system. The β_1-adrenergic and the D_1-like dopamine receptors are linked to phospholipase C; stimulation leads to an increase in formation of inositol phosphates and diacylglycerol. Inositol phosphates increase intracellular calcium while diacylglycerol stimulates protein kinase C. Occupation of β_1-adrenergic and D_1 dopamine receptors may also result in the activation of phospholipase A_2 increasing the formation of biologically active arachidonate metabolites by the action of cyclooxygenases (prostaglandins, thromboxanes), lipoxygenases (leukotrienes), and cytochrome p450 monooxygenase (e.g., 20 hydroxyeicosatetraenoic acid).

Receptor regulation. Signal transduction involves "on" and "off" pathways to ensure that signaling is achieved in a precisely regulated manner *(55–57)*. One "off" pathway is receptor desensitization or loss of receptor responsiveness. Receptor desensitization is a mechanism to dampen short-term agonist effects following repeated agonist exposure. Desensitization involves several processes, including phosphorylation, sequestration/internalization, and degradation of receptor protein *(55–57)*. An initial step in the desensitization process is the phosphorylation of the receptor by a member or members of the G protein-coupled receptor kinases (GRKs) family. GRKs are serine and threonine kinases that phosphorylate G protein-coupled receptors (GPCRs) in response to agonist stimulation. The phosphorylation of GPCRs, including D_1 receptors, leads to the binding of a member or members of the arrestin family, an uncoupling of the receptor from its

G protein complex and a decrease in functional response *(55–58)*. The phosphorylation of β-arrestin 1 or β-arrestin 2 inhibits while *S*-nitrosylation of β-arrestin 2 but not of β-arrestin 1 promotes clathrin-mediated internalization of certain GPCRs (e.g., β2-adrenergic receptor). β-arrestin 2 acts as a scaffold linking endothelial NO synthase (eNOS) with β2-adrenergic receptor, a fast recycling class A receptor, and slow recycling class B receptors (e.g., AT_1 receptor). The *S*-nitrosylation of dynamin promotes scission of the endocytosed clathrin–GPCR complex, resulting in GPCR internalization. A discrete pool of eNOS *S*-nitrosylates GRK2 upon ligand stimulation and allows for the fast recycling of class A receptors *(59,60)*. The phosphorylated GPCR and arrestin complex undergoes internalization via clathrin-coated pits into an endosome where the GPCR is dephosphorylated *(61)*, facilitated by protein phosphatases, and recycled back to the plasma membrane or degraded by lysosomes and/or proteasomes *(62)*. These processes may be specific to a particular receptor. It should also be noted that the binding of certain GPCRs (protease-activated, orexin, substance P, and leukotriene B4 receptors) to arrestin is phosphorylation independent *(63)*.

Development of receptor regulation. There are developmental changes in the desensitization process. The neonatal rat heart is resistant to β-adrenergic receptor desensitization *(64)*. Rather, β-adrenergic agonists produce sensitization caused by the induction of adenylyl cyclase activity as a consequence of loss of $G\alpha_i$ protein and function, enhancement of membranous expression of $G\alpha_s$, and, in particular, the shorter but more active 45-kDa $G\alpha_s$. The role of Gβ/γ was not determined but in the kidney we found that the decreased inhibitory effect of D_1 receptors on the sodium hydrogen exchanger type 3 is caused by increased expression and linkage of the G protein subunit Gβ/γ *(65)*.

Catecholamines and other vasoactive agents. Catecholamines can influence blood pressure not only by direct effects on resistance vessels but also, indirectly, by modulating the secretion of other vasoactive agents such as angiotensin II (via renin), vasopressin, prostaglandins, substance P, and other neuropeptides. In addition to direct chronotropic and inotropic effects on the heart, catecholamines can modulate CO indirectly by affecting blood volume and venous return. Blood volume can be regulated by direct effects on sodium and water transport through renal nerves, by antagonizing effects of other hormones (e.g., vasopressin), and indirectly by modulating vasopressin and aldosterone secretion.

ADRENERGIC SYSTEM DURING DEVELOPMENT

The low systolic blood pressure at birth, due to low CO and peripheral resistance, increases rapidly in the first 6 weeks of life, remains at a constant level until age 6 years, and increases gradually until age 18 years. The pattern is similar for diastolic blood pressure except that there is a slight decrease in diastolic blood pressure in the first 6 months of life (relative to the blood pressure in the first week of life). The increase in blood pressure with age in preterm infants occurs as a function of postconceptional age. With advanced age (>60 years), systolic blood pressure continues to increase but diastolic blood pressure declines some, leading to an increase in pulse pressure. Increased pulse pressure plays an independent role in the pathogenesis of the complications of high blood pressure *(66)*. The increase in blood pressure with age is due to a rise in both CO and total peripheral resistance. The age-related changes in vascular resistance are selective because in the perinatal period there is a rapid fall in resistance in the lungs, small intestines, brain, and the kidney while resistance increases in the femoral vessels *(67)*. The increase in femoral resistance with age is

probably related to an increase in vascular reactivity to vasoconstrictors with no differential effects of vasodilators (nitric oxide and bradykinin). The decrease in regional vascular resistance may be caused by an increase in vessel growth and changing sensitivity and reactivity to vasoconstrictor and vasodilator agents (see below). The increase in regional blood flow with age cannot be accounted for by an increase in blood pressure. Indeed, in the immediate perinatal period, the increase in regional blood flow with postnatal age is independent of blood pressure *(68)*. In the first 6 months of life, systolic blood pressure increases but diastolic blood pressure actually decreases after the first 2 weeks of life. This transient decrease in diastolic blood pressure in the first few months of life is associated with a low intestinal vascular resistance *(69)*. This is apparently mediated by NO. Interestingly, increased NO production, presumably from neuronal NO synthase, as well as increased expression of angiotensin type 2 receptor, in the neonatal renal arterial bed *(70–72)* also dampens the increased vasoconstriction afforded by angiotensin II, early in perinatal life and catecholamines later *(73)*. NO, however, does not play an important role in cerebrovascular responses in the newborn.

The newborn infant increases its CO mainly by increasing heart rate. The high heart rate may be due to differential sympathetic and parasympathetic effects, hypersensitivity of the cardiac receptors, and peripheral vasodilatation. The low precapillary resistance and low venous capacitance are conducive to high systemic blood flow per unit body weight and provide increased tissue perfusion for growth.

Study of the role of the adrenergic nervous system in the control of cardiovascular dynamics is complicated by species differences. Some studies have suggested that pigs and dogs provide the closest model to the newborn human in terms of cardiovascular development *(72,73)*. On the other hand, the sheep fetus is a very useful model for chronic conscious studies *(74,75)*. These considerations are important because the changes in maternal diet or intrauterine events can affect blood pressure of the offspring as an adult *(76–79)*.

DEVELOPMENT OF THE SYMPATHETIC NERVOUS SYSTEM

The development of the sympathetic nervous system can be divided into three stages *(80)*. In the first stage, the neural crest cells migrate to their positions within the body tissues. In the second stage, the cell number and type are refined by cell death (apoptosis). The third stage is concerned with the maturation of synaptic connections and selection of the neurotransmitter. There are several factors that are involved in these processes and involve the interactions of several genes and growth factor families. A very important family, the neurotrophin family of growth factors, controls autonomic development, including nerve growth factor, brain-derived neurotrophic factor, and neutrophins 3 and 4 which act via high-affinity Trk receptor tyrosine kinases A, B, and C and lower affinity neurotrophin receptor p75 *(81)*. Ventral migration of neural crest cells is controlled by neuregulin-1; neuroblast survival and differentiation by hepatocyte growth factor; neural crest cell migration and sympathetic ganglion formation by semaphorin 3A; induction of noradrenergic differentiation by bone morphogenetic protein (BMP) family members, BMP-2 and BMP-7; and the noradrenergic phenotype by transcription factors Mash1, Phox2a and b, Cash1, dHand, and GATA-3 *(82,83)*. Cholinergic development generally takes place prior to adrenergic differentiation *(83)*; however, transition from adrenergic to cholinergic function can also occur. The cholinergic differentiation factors remain to be identified but may include the neurotrophins, such as neurotrophin-3, and glial-cell-derived neurotrophic factors, such as neurturin and receptors, such as glial cell line-derived neurotrophic factor family receptor

alpha-2 *(7,81–83)*. In the neonatal rat heart, perinatal β-adrenergics positively regulate the development of sympathetic innervation and suppress the development of m_2 muscarinic acetyl choline receptors *(84)*. A critical event in the development of the adrenergic nervous system is the establishment of functional innervation of the different organs. Function requires that central nervous pathways to the preganglionic neurons be established, that information be relayed to postganglionic neurons, and that neurotransmitter synthesis, release, and reuptake and postreceptor mechanisms be operative. Effector organ innervation involves the outgrowth of new axons, appearance of intense fluorescence, and differentiation of adrenergic nerve varicosities. Maturation of the nerve terminal–effector complex occurs before ganglionic transmission is fully developed and is largely independent of neural connections. In the heart, the development of β-adrenergic receptors and their responsiveness to catecholamines are not closely linked to innervation. Nonsympathetic hormonal factors appear to control early maturation of receptors and the growth and development of the nervous system.

Plasma catecholamines. Plasma norepinephrine and dopamine levels decrease gradually with advancing gestational weeks *(85)*. Birth is associated with an increase in circulating catecholamines. Umbilical arterial epinephrine and norepinephrine concentrations in infants delivered vaginally are greater than those in infants delivered by cesarean section *(86–88)*. Because there are some studies showing no difference in plasma concentrations between infants delivered vaginally and those by cesarean section *(89,90)*, stress per se may not responsible for the high catecholamine levels with vaginal delivery. Studies in the fetal sheep indicate a surge in plasma catecholamines with the onset of parturition that is accentuated by cord cutting *(91)*. The half-life of circulating catecholamines in the preterm infant may be longer than in older children, due in part to lower levels of catecholamine-degrading enzymes. However, children may metabolize catecholamines more rapidly than adults. Preterm infants have greater levels of epinephrine in umbilical arterial plasma than full-term human infants. Preterm fetal sheep also have higher circulating catecholamine levels than their full-term counterparts. The circulating levels of catecholamines decrease with maturation, but beyond 20 years of age plasma norepinephrine increases. Adrenal medullary activity is lower than adrenergic nervous activity at birth and increases with maturation. Neonatal blood pressure waves have been reported to be associated with surges of systemic norepinephrine *(92)*.

Urinary catecholamines. Urinary catecholamines are low at birth and increase with gestational and postnatal age *(93–95)*. Small-for-gestational-age babies have greater sympathoadrenal activity than babies of the same gestational age *(93)*. Newborn preterm infants excrete less norepinephrine and more dopamine than term infants; epinephrine excretion is comparable. At 2 weeks of age, urinary dopamine and metabolites are greatly increased in preterm infants. Beyond 1 year of life, the developmental patterns of adrenergic nervous and adrenal medullary activity are similar and reach mature values at 5 years of age. When expressed as a function of surface area or weight, no changes in urinary catecholamines and metabolites occur after 1 year of age. In the first 5 years of life, however, sympathoadrenal activity is less in girls than in boys. It should be kept in mind, though, that circulating and urinary levels of catecholamines are only rough indices of adrenergic activity. Preadolescent and early adolescent children, especially females, born prematurely or small for gestational age have higher circulating and urinary catecholamine levels than their term and weight appropriate for gestational-age counterparts *(96,97)*.

Catecholamines and adaptation to extrauterine life. Catecholamine secretion at birth may be important in the adaptation of the fetus to extrauterine life *(91,67)*. Complete

ganglionic blockade before delivery of the lamb does not attenuate the normal postnatal rise in blood pressure, indicating that the autonomic nervous system may not play a significant role in the increase in systemic pressure after birth. However, although clamping of adrenal vessels did not alter mean blood pressure of very young puppies *(99)*, in the newborn dog adrenalectomy leads to hypotension and bradycardia. In addition, adrenergic blockade in the newborn lamb reduces systemic pressure, whereas no effect is seen in adult sheep. Other proofs for the importance of the adrenergic nervous system during the neonatal period include both impaired myocardial contractile responses to adrenergic agents and hypoxia after adrenalectomy.

The time of development of adrenergic innervation and responses to adrenergic stimulation varies not only with species but also among vessels in the same animal. Some of the reported differences in results may also be due to experimental conditions (anesthetized versus unanesthetized state, in vitro versus in vivo studies). In the heart, responses to β-adrenergic and dopamine stimulation increase with age while the response to α-adrenergic stimulation decreases with age. While the decreasing responsiveness to β-adrenergic stimulation with maturation has been linked to similar directional changes in myocardial α_1-adrenergic receptors, the changes in myocardial β-adrenergic receptors are not linked. For example, in the dog heart there is an increased β-adrenergic receptor density in the newborn period. The decline in cardiac β-adrenergic receptors density with age is accompanied by decreased β-adrenergic responsive adenylyl cyclase activity. Other studies, however, have shown that cardiac β-adrenergic receptors increase with age but the proportions of β-adrenergic subtypes do not.

In the mature heart, responsiveness to β-adrenergic agonists can be regulated transsynaptically by neurotransmitter concentrations in the synaptic cleft. High levels of β-adrenergic stimulation result in depressed cardiac responsiveness and reduction in receptor density (downregulation) while the converse occurs with low levels of stimulation with upregulation of receptor density. However, this does not occur during the period in which receptor numbers and cardiac sensitivity to agonists are undergoing marked developmental increases. The developmental changes in cardiac responsiveness to dopamine have not been correlated with dopamine receptor density or adenylyl cyclase activation.

Regional vascular flow and resistance during development. The development of renal and intestinal circulation is discussed in some detail because splanchnic vascular resistance contributes significantly to peripheral vascular resistance. β-Adrenergic relaxation of the aorta of rabbits increases with age, reaching a maximal level at 1 month; thereafter a decline in responsiveness occurs. In dogs, stimulation of lumbar sympathetics induces femoral vasodilatation early in life; after 2 months a greater vasoconstriction is noted. This corresponds to a marked increase in adrenergic innervation. In the piglet, the renal vascular response to β-adrenergic stimulation is also less in the immediate newborn period compared to adults but may be markedly increased some time before maturation *(99)*. These changes in renal β-adrenergic responsiveness have been correlated with β-adrenergic receptor density in the dog *(100)*. However, β_2-adrenergic vasodilatory effects are enhanced in the renal vascular bed of the fetal lamb *(100)*.

The maturation of blood vessel reactivity to β-adrenergic stimulation is regional bed dependent. In general, during the neonatal period there is a lesser responsiveness of the canine aorta and sheep carotid to norepinephrine compared to the adult. This occurs in spite of comparable responsiveness to KCl *(101)*. The vasoconstrictor effects of α-adrenergic drugs are also less in immature than mature animals. In the neonatal rat femoral artery, norepinephrine causes a vasodilation rather than vasoconstriction, an effect mediated by

nitric oxide *(102)*. In baboons, the maximum vasoconstrictor response to norepinephrine, thromboxane mimetic, and potassium increased with gestational age, but the sensitivity to these vasoconstrictors was similar *(67)*.

Renal vascular bed. Renal blood flow increases progressively with conceptional age reaching term values by about 35 weeks postconception. Forty weeks postconception renal blood flow expressed as a function of surface area increases with postnatal age reaching middle-age adult values by 1–2 years of life. The increase in renal blood flow is associated with a fall in renal vascular resistance. Color Doppler ultrasonography has been used to determine renal resistive index, which correlates with renal vascular resistance. In general, the values obtained using clearance methods (e.g., para-aminohippurate) have correlated well by the renal resistive index *(103)*. The increase in renal blood flow with age is due to renal growth, an increase in blood pressure, and a decrease in renal vascular resistance. The high renal vascular resistance in the perinatal period has been shown to be caused by alterations in renal vascular smooth muscle reactivity and sensitivity to vasodilators and vasoconstrictors. After the immediate newborn period, the neonatal renal and cerebral circulation are more sensitive to α-adrenergic stimulation in dogs, pigs, guinea pigs, and baboons *(72,104,105)*. The isolated renal vessels of fetal lamb studied in vitro and in vivo are also more reactive to β-adrenergic stimulation than their newborn or adult counterparts *(106)*. The increased renal α_1- and α_2-adrenergic effects in fetal sheep are related to increased α-adrenergic receptor density. Competition experiments and rank adrenergic antagonist potency suggested the presence of only the α_{1B}-adrenergic receptor in fetal and adult sheep kidneys. However, α_{1B}-adrenergic receptor does not mediate vasoconstriction in adults. The α_2-adrenergic receptor that was found only in the fetal sheep had a low affinity to rauwolscine, which is unlike that described in most species for α_2-adrenergic receptors *(107)*. However, the molecular biological class of these receptors during development has not been studied.

Inherent renal vascular hypersensitivity or hyperreactivity may be masked by counterregulatory vasodilator mechanisms. In the fetal sheep renal vascular β_2-adrenergic receptor-mediated renal vasodilatory capacity is enhanced during fetal life *(108)*. Cerebral arteries from premature and newborn baboons showed a more marked relaxation response to isoproterenol than did arteries from adult animals *(104)*. In the piglet, the renal vasoconstrictor effects of angiotensin II are counteracted by vasodilatory action of nitric oxide *(70,71,109)*. However, the contribution of specific adrenergic receptors and regulation of nitric oxide level or availability to the development of renal circulation remain to be determined.

The neonatal renal circulation is also more responsive to the effects of renal nerve stimulation in some species *(110)*. While renal nerve transection in piglets leads to an increase in renal blood flow *(110)*, this effect is not seen in fetal sheep. Moreover, renal nerve stimulation during α-adrenergic blockade actually increases renal blood flow *(101)*. In the neonatal dog kidney, increased α-adrenergic effects are related to increased β-adrenergic receptor density *(111)*. Dopamine mainly induces a vasoconstrictor response (an β-adrenergic receptor effect) in the early neonatal period *(111)*. Even low dosages, which produce renal vasodilatation in the adult kidney, are associated with renal vasoconstriction in the newborn period. The vasodilator effects of dopamine become evident in the femoral circulation before being noted in the kidney. When β- and β-adrenergic receptors are blocked during dopamine infusion, the renal vasodilator effect of dopamine is still less in the fetus and the newborn animal compared to the adult. In contrast to the correlation between renal vascular responses and β- and β-adrenergic receptor density, no correlation is observed with dopamine receptors and the age-related changes in renal dopamine responsiveness.

The low renal blood flow in the young is due to several factors, including smaller size, decreased number of glomeruli, lower systemic pressure, and higher renal vascular resistance. The increased renal vascular resistance in the newborn is probably due to increased activity of the renin–angiotensin system as well as increased sensitivity to vasoconstrictor catecholamines. The latter is due to receptor and postadrenergic receptor mechanisms. Critical vasodilators, such as nitric oxide, may act to counterbalance these vasoconstrictor forces. The increase in renal blood flow with age presumably occurs as the vasoconstrictor influences decline. Adult growth-restricted offspring develop hypertension that may be caused by increased renal nerve activity *(112)*.

Intestinal vascular bed. Intestinal blood flow, like renal blood flow increases with gestational age, postconceptional age, and maturation *(113)*. Fetal intestinal vascular resistance is high during fetal life. In the piglet, there is a further decrease in intestinal vascular resistance in the first few days of life, only to progressively increase after the first week of life. This is in contrast with kidneys in which there is a progressive decrease in renal vascular resistance in the perinatal period. The neonatal intestinal circulation is controlled by inherent myogenic response and nitric oxide similar to that seen in the neonatal renal circulation. Like the neonatal kidney neonatal intestinal circulation may also be regulated by alterations in α-adrenergic receptor *(114)*. However, in contrast to the neonatal kidney, endothelin plays a part in the regulation of neonatal intestinal circulation. In older piglets, regulation of the intestinal circulation does not involve nitric oxide or endothelin, the responses being mainly passive in nature *(69,115)*. In contrast to importance of nitric oxide in the renal and intestinal vasodilator response in the newborn, bradykinin and prostanoids perform this role in the neonatal cerebral vascular bed *(116)*. However, with maturation nitric oxide assumes a more important role.

CONCLUSION

In summary, increase in blood pressure with age in the first few months of life is mainly due to an increase in cardiac output. Vascular resistance in many vascular beds may transiently decrease because of increased production or availability of nitric oxide, prostanoids, or increased sensitivity to β-adrenergic stimulation. The involvement of a particular agent is regional bed dependent. While the maturation of receptor classes involved in the regulation of cardiac output and vascular resistance is known, the maturation of specific receptor subtypes in different vascular beds remains to be determined.

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4 Ion and Fluid Dynamics in Hypertension

Avram Z. Traum, MD

Contents

Among the many determinants of blood pressure, ion transport has played a key role in both the basic understanding and the 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 the control of moderately elevated blood pressure *(3,4)*. In addition to sodium restriction, the role of natriuresis has been translated into pharmacologic 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. These genes typically encode proteins that affect renal tubular sodium handling, reviewed elsewhere in this text. 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, these comprise only a small fraction of the overall burden of hypertension. More broadly, however, pathogenic changes in ion transport have been implicated both in 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 some of the ion channels studied in

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_4
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hypertension and their relevance to clinical practice. Both channel function and structure will be considered.

SODIUM CHANNELS

Given the importance of salt in the management of blood pressure, sodium channels have been extensively studied as targets both in animal models of hypertension and in clinical research.

All relevant channels expressed along the length of the tubule have been studied. These include a variety of transporters of sodium: the Na^+/H^+ exchangers (NHEs), the $Na^+-K^+-2Cl^-$ cotransporter (NKCC), the Na^+-Cl^- cotransporter (NCC), as well as the epithelial sodium cotransporter (ENaC), the sodium–potassium ATPase (Na^+/K^+ ATPase), and the sodium–phosphate transporter (NaPi II) (see Table 1).

Table 1
Sodium Channels of 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
Sodium–phosphate transporter (NaPi II)	Proximal tubule	Apical

NHE Transporters

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

NHE1 activity is increased in the SHR in multiple cell types, including RBCs, platelets, leukocytes, skeletal muscle, vascular smooth muscle cells, and tubular epithelial cells. This effect was not seen in RBCs or proximal tubular cells of a second rat model of essential hypertension, the Milan hypertensive strain (MHS). RBC Na^+/H^+ transport has been examined in humans as well and appears to correlate with renal sodium retention in hypertensive individuals *(7)*. The differential effect in SHR versus MHS strains aligns well with human studies, as approximately half of the patients studied had increased RBC Na^+/H^+ activity *(8,9)*. This increased Na^+/H^+ activity likely reflects a systemic effect as it has also been demonstrated in skeletal muscle both in SHR *(10)* and in humans with essential hypertension *(11)*.

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 *(12)*, though mRNA expression is not altered. However, this enhanced activity may be related to decreased expression of the NHE regulatory factor 1 (NHERF1) *(13)*, which normally inhibits the activity of NHE transporters, suggesting that NHE3 changes are unrelated to gene expression or structure per se. Kelly et al. *(14)* studied the relative contributions to sodium transport of NHE1 and NHE3 in proximal tubule cells of SHR. Their studies revealed equal activity of both proteins. While NHE1 protein expression was similar to that of normotensive wild-type controls, NHE3 expression was increased by 50% in SHR. An earlier study *(15)* of the NHE3 knockout mouse showed findings of proximal renal tubular acidosis with salt wasting, polyuria, and lower blood pressure, in spite of rise in renin expression and 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. *(16)* studied polymorphisms in *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.

NKCC Transporters

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

The importance of NKCC2 is related primarily to its role in net sodium and chloride reabsorption in the thick ascending limb of the loop of Henle and its inhibition by diuretics such as furosemide. This transport system is responsible for approximately 25% of tubular sodium reabsorption. Lifton's group *(17)* reported that mutations in the gene encoding the NKCC2 protein (*SLC12A1*) cause type 1 Bartter syndrome, a severe manifestation of Bartter syndrome that has antenatal manifestations with polyhydramnios, prematurity, and postnatal electrolyte wasting and volume depletion. Biochemically, the hallmark of this disease is elevated plasma renin activity and aldosterone level with low to normal blood pressure. Perhaps more clinically relevant are studies by the same investigator group identifying mutations in genes encoding NKCC2, NCCT, and ROMK, which appeared to be protective against hypertension from subjects in the Framingham Heart Study *(18)*.

Similar to NHE transporters, NKCC has also been studied in RBCs in animal models and in humans with hypertension. There is higher activity in RBCs in MHS rats compared with controls, and these animals demonstrate a greater natriuretic response to bumetanide *(19)*. Since this strain has normal expression of NKCC2 mRNA and protein *(20)*, 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 *(21–23)*. However, these patients also have an exaggerated response to furosemide *(24)*.

The NCCT

Given the widespread use and success of thiazides in treating essential hypertension, the sparse data on this transporter in both animal models and human hypertension are surprising. Capasso et al. *(20)* demonstrated increased expression of the NCCT in MHS rats, in

contrast to NKCC2 and NHE3 mRNA expression. Mutations in the NCCT gene (*SLC12A3*) were also found to be protective against the development of high blood pressure in Framingham Heart Study subjects *(18)*.

ENaC

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

The Dahl salt-sensitive rat strain has been shown to exhibit increased activity of intrarenal ENaC. Specifically, in cell cultures of collecting ducts from these strains, sodium transport was enhanced as compared to control strains and was augmented by aldosterone and dexamethasone *(25)*. 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 *(26)*.

As noted, Liddle syndrome is caused by mutations in the genes encoding the β- and γ-subunits of ENaC. These mutations result in truncated proteins without 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. *(27)* studied β-ENaC variants in hypertensive families. After determining the most common changes observed in the last exon, they assessed the frequency in a French cohort of 525 patients. Although these changes were seen in only 1% of whites, the frequency increased up to 44% in those of African ancestry. However, only a fraction of those variants led to changes in sodium flux when studied in *Xenopus* oocytes *(27)*.

A relatively common variant in β-ENaC, T594M, has been examined in a number of studies. This variant was first reported by Su et al. *(28)* 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 *(29)*. A second study identified an association between this same variant and hypertension in 348 blacks in a study from the UK *(30)*. 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 *(31)*. Moreover, administration of amiloride to those with this variant did not demonstrate any differential effect as compared to those with wild-type β-ENaC. Thus, the role of ENaC variants in essential hypertension remains to be fully elucidated.

Na^+/K^+ ATPase

This ubiquitous pump generates the driving force for a myriad of transport processes. In the renal tubule, the pump results in net sodium gain, allowing epithelial sodium reabsorption along the length of the renal tubule. Earlier studies revealed increased Na^+/K^+ ATPase activity in MHS kidney extracts as compared with controls *(32)*. 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 *(33)*.

In contrast to primary overactivity of this pump, Blaustein et al. *(34)* 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 *(35)*. 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 *(36)*. An endogenous ouabain-like substance has been isolated from MHS and mammalian hypothalamus *(37)*.

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 *(38)*. The resulting rise in intracellular calcium improves contractility in cardiac myocytes and vascular smooth muscle cells (VSMCs). This link has been further established on a cellular compartment level with colocalization of Na^+/K^+ ATPase and NCX.

It should be noted that differing Na^+/K^+ ATPase subtypes likely mediate this effect, with α2 subtypes having the greatest affinity for endogenous ouabain and its effect on VSMCs *(39,40)*. In mice, expression of the α2 subtype with a shortened N terminus is dominant negative for expression of wild-type full-length α2 pumps *(41)*. When this dominant-negative α2 pump was expressed using a smooth muscle-specific myosin promoter, reduced pump function and elevated blood pressure were observed *(34)*. Conversely, mice that overexpress the α2 pump within smooth muscle have significantly lower blood pressure than α2 wild-type mice and mice with α1 overexpression *(42)*.

The relationship between these transporters suggests a sequence by which increased salt and water intake leads to volume expansion, followed by secondary release of endogenous ouabain *(34,43)*. The inhibition of the Na^+/K^+ ATPase attempts to prevent further sodium retention by the kidneys. Within VSMCs, this phenomenon 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 *physiologic levels of ouabain* on the different pump isoforms. 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 *(44,45)*. This differential effect on isoforms of the Na^+/K^+ ATPase leads to a net increase in blood pressure *(46)*.

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 steroid 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 control rats treated with ouabain, deoxycorticosterone acetate, and salt-treated rats in a remnant kidney model *(46,47)*. This effect has not yet been studied in humans *(48)*, although it presents an opportunity to link the basic research done in this model with clinical care.

REGULATION OF ION FLUX

While multiple channels have increased activity that leads to 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 in these models have provided conflicting data. However, the cytoskeleton has been implicated as having a role in this altered functional activity. For example, adducin is a component of the cytoskeleton and is ubiquitously expressed. It is found in both rats and humans, and its association with salt-sensitive hypertension has been described in both.

Adducin mutations in both α- and β-subunits have been associated with hypertension in MHS rats *(49)*. A follow-up study by this group showed that in rat tubular epithelium, adducin mutations increase Na^+/K^+ ATPase activity *(50)*. They later described that MHS rats with these mutations did not have the expected endocytosis of Na^+/K^+ pumps in response to dopamine *(51)* and may reflect a broader alteration in clathrin-dependent endocytosis *(52)*. Other groups have shown that in a variety of rat models of hypertension, genes encoding adducin subunits have been found within quantitative trait loci for hypertension *(53)*. Rostafuroxin reduces blood pressure in hypertensive MHS rats with adducin mutations as well *(46,47)*.

α-Adducin polymorphisms have been described in salt-sensitive hypertension as well. In an Italian study of 936 persons, including hypertensive siblings, hypertensive individuals, and normotensive controls, the G460W polymorphism was studied, with a significant association seen in this population *(54)*. Interestingly, this relationship was not seen in a cohort of 375 Scottish patients *(55)* or 507 Japanese patients *(56)*.

CONCLUSIONS

Aberrant ion transport is a critical component in the pathogenesis of hypertension. The research presented reflects only a subset of the published data in this field. It also represents an exciting area of potential study in children and adolescents with essential hypertension, many of whom are salt sensitive. The role of rostafuroxin has yet to be established in the treatment of hypertension, but establishes a new class of agent that more directly targets essential hypertension without the complicating metabolic side effects of thiazides.

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5

CRP, Uric Acid, and Other Novel Factors in the Pathogenesis of Hypertension

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Contents

INTRODUCTION

Hypertension is one of the most common diseases in the world. In Western countries, it affects between 20 and 75% of the adult population, depending on age, and is not only the most important risk factor for cardiovascular and renal disease but is also the most amenable to modification with current medical therapy *(1)*. In adult populations, the vast majority of hypertension is essential hypertension, so that standard recommended practice is not to do extensive evaluation for the secondary etiologies of hypertension at the time of diagnosis *(1)*. While this practice saves money, it compromises the ability of epidemiologists to identify mechanistic risk factors, as all hypertensive populations considered as essential hypertension are contaminated with patients with secondary hypertension of various etiologies, including monogenic conditions, renal parenchymal disease, hyperaldosteronism, renovascular disease, and others.

Childhood hypertension, increasingly common, offers an opportunity to gain insights into the early pathophysiology of what is currently called essential (primary) hypertension.

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_5
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Because secondary hypertension is more common among children with elevated blood pressure than in adults, the current clinical guidelines, detailed in Chapter 28, include detailed testing and evaluation to distinguish secondary from essential hypertension *(2)*. Such evaluation results in clearer case definition of essential hypertension among children. Further, children have fewer confounding diagnoses such as diabetes, atherosclerotic heart disease, and age-related illness, making children and adolescents the ideal population in which to study the early physiological steps that initiate essential hypertension. Studies of newly hypertensive patients also allow investigators to distinguish factors involved in initiating hypertension from those caused by persistent, chronic hypertension.

This chapter describes some of the nonconventional risk factors for hypertension. For most, the data are exclusively observational and require much more laboratory and clinical study before these factors can be considered potential therapeutic targets. In a few cases, however, the data provide a more complete pathophysiological story. This chapter emphasizes the potential roles of C-reactive protein (CRP) and uric acid in the development of hypertension, not because these should be considered major risk factors for essential hypertension, but because studies of these factors are further advanced than some of the other potential risk factors, so that such studies may serve as a model for investigating other potential novel causes of the development of hypertension.

GENETIC POLYMORPHISMS ARE AN INSUFFICIENT MODEL

Several models have been developed to support the concept of hypertension as a disease of renal sodium handling. In fact, the tendency toward sodium retention and sodium sensitivity is a common aspect of hypertension in adults and children *(3,4)*. A favored hypothesis is that hypertension results from a polygenic defect in which there are alterations in the regulation or expression in tubular transport systems involved in sodium reabsorption and excretion *(5,6)*. The discovery that many forms of genetic hypertension are associated with enhanced sodium reabsorption has provided support for this hypothesis *(5,6)*. However, studies using conventional genetic methods as well as others using genome-wide association methods suggest that known genetic mechanisms can only account for a minority of cases of hypertension *(7,8)*. Furthermore, a study of 1003 identical twins found that when one twin was hypertensive, the other was hypertensive only 44% of the time *(9)*, which strongly argues against hypertension being a typical monogenetic or polygenic defect. Even more convincing are epidemiologic data that show a dramatic increase in the prevalence of hypertension over the past 100 years. Thus, studies in the early 1900s showed a near absence of hypertension in Africa, Asia, Arabia, South America, Australia and New Zealand, and Oceania (reviewed in *(10)*), but now hypertension is rapidly increasing in prevalence along with the worldwide epidemic of obesity and diabetes *(11)*. Similarly, hypertension was observed in only 10% of the population in the USA in the early 1930s *(12)*, but is now present in over 30% of the population *(13)*. It is difficult to explain how a purely genetic mechanism could account for this rapid change in prevalence. Finally, a genetic defect in sodium excretion as a primary mechanism for essential hypertension does not easily account for studies that show that in early hypertension blood volume and exchangeable sodium tend to be low *(14–16)*, that early hypertension is frequently salt-resistant (i.e., is not altered by sodium intake) *(17)*, and that salt sensitivity increases progressively with aging *(17)*. Consequently, a model that fully explains hypertension must include the effects of peri- and postnatal life, and exposures and effectors that alter vascular physiology after organ development is complete.

PRENATAL EXPOSURES

A nongenetic prenatal or developmental predisposition to hypertension has been hypothesized for a number of years *(18)*, based on both epidemiological and experimental observations (also see Chapter 13). First, there is evidence for a 'maternal factor' in hypertension, because hypertension is inherited more commonly through the mother than the father *(19)*. Indeed, a child's risk of hypertension is increased if the mother has hypertension, preeclampsia, obesity, or malnutrition during pregnancy *(20)*, each of which increases the risk for delivering a low birth weight baby; lower birth weight is associated with increased risk of hypertension during adulthood *(20)*. Lower birth weight associated in experimental models and, possibly, in humans, with fewer nephrons owing to impaired nephrogenesis *(21)*. In support of this hypothesis is the observation that the experimental induction of malnutrition during pregnancy in rats results in pups that are born with low nephron number and later develop salt-sensitive hypertension *(22)*. Autopsy studies of young hypertensive subjects dying from traffic accidents have also verified that the kidneys have significantly fewer nephrons than those of age-matched normotensive controls *(23)*. However, while low birth weight is especially common among African-Americans *(24)*, who have the greatest risk for hypertension in the United States, available data does not support a decreased number of nephrons. Despite strong evidence for perinatal effects, most patients who develop hypertension as adolescents or adults lack obvious pre- and perinatal risk factors. Consequently, later-acting effectors must be considered.

CRP AND HYPERTENSION

Over the past two decades a great deal of interest has focused on the role of inflammation in cardiovascular disease, particularly in atherosclerosis. A variety of protein biomarkers of ongoing inflammation can be measured in the bloodstream and have been studied as potential markers or predictors of future risk of CV events. Among such biomarkers, there is substantial evidence that C-reactive protein, beyond its tracking with ongoing inflammation, may be a marker and participant in vascular disease and/or hypertension *(25)*.

Assays to measure CRP and their interpretation have evolved over time. The original tests, used for research and clinical evaluation in the early 1990s, were developed for patients with infections and inflammatory disorders and have a detection range from 3 to 20 mg/L, well above the levels expected in healthy persons. Most laboratories now use a highly sensitive C-reactive protein (hsCRP) assay that has a linear detection range down to 0.3 mg/L. Actual values that constitute an abnormal elevation are the topic of debate and can vary from lab to lab. The Centers for Disease Control (CDC) and American Heart Association (AHA) have produced consensus definitions that hsCRP values of <1, 1–3, and >3 mg/L define the population tertiles in adults and consider values >10 mg/L as abnormal in any patients *(26)*. When CRP is measured for risk screening, the optimal technique is to use the average of two tests, at least 2 weeks apart, with a mean value of >3mg/L indicating increased CV risk *(25)*.

A possible link between CRP and atherosclerotic cardiovascular disease is controversial. Animal models show that infusion of CRP increases aortic plaque area *(27)*; CRP through activation of complement *(28,29)* can exacerbate myocardial ischemic injury *(30,31)*. In a small clinical study, seven volunteers were infused with CRP, which resulted in a transient rise in IL-6, IL-8, serum amyloid A, and several procoagulation molecules *(32)*. Larger clinical and epidemiological trials less consistently support a direct role for CRP in CV

disease. Among a cohort of 50,000 adults with and without history of ischemic CV disease, persons with CRP >3 mg/L had a 1.6-fold increase in relative risk of CV events as compared to those with levels <1 mg/L *(33)*. In the same study, four genetic polymorphisms of CRP accounted for more than 60% of the variability in serum levels of CRP, yet combined polymorphisms expected to confer greater risk did not. Other studies of polymorphisms considered as high risk were also unassociated with CV risk *(34–37)*. As most studies have suggested elevated CRP is associated with risk while mechanistic studies have been inconsistent, most experts consider CRP as a marker but not a mediator of cardiovascular disease *(26)*. In children several studies have correlated CRP with CV risk *(38,39)*, metabolic syndrome *(40)*, and left ventricular hypertrophy *(41)*. It has also been noted to be higher in the offspring of parents with essential hypertension *(42)*.

The central hypothesis regarding a role of CRP in the etiology of hypertension is that it induces endothelial dysfunction and increased vascular reactivity through perivascular inflammation. CRP is an acute-phase protein that is produced predominantly in the liver under transcriptional regulation directed by inflammatory cytokines. Several studies have shown the induction of production and elaboration of CRP by interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) *(43,44)*. Addition of recombinant CRP to the growth medium of cultured endothelial cells results in the reduction of NO production, which could result in reduced vasodilation *(45,46)*. In cultured vascular endothelial cells, CRP induces production and elaboration of endothelin-1, a potent vasoconstrictor *(47,48)*. Finally, CRP increases the surface expression of angiotensin II type 1 receptors on vascular smooth muscle cells *(49)*, making them more responsive to the vasoconstrictive action of angiotensin II (Ang II. While all of these experimental mechanisms are plausible pathways to hypertension, none have been confirmed in humans.

The epidemiologic evidence suggesting a link between CRP and hypertension is not definitive. The strongest evidence for a link comes from the Women's Health Study, in which 20,525 women >45 years in age were followed for 10 years. The total incidence of hypertension during the follow-up period was 26%. Baseline hsCRP was linearly associated with incident hypertension as a statistically significant independent risk factor (relative risk 1.31–2.32, depending on age and other factors) *(50)*. Likewise, an analysis of the National Health and Nutrition Examination Survey II (NHANES-II) indicated that CRP was an independent risk factor for incident systolic hypertension in girls, aged 12–17 years *(51)*. A recent bivariate analysis of the NHANES-III data reported that participants with CRP >3 mg/L had higher systolic but not diastolic blood pressure as compared to those with CRP <3 mg/L. Multiple regression analysis found that this effect was independent of other CV risk factors only in black boys and was of relatively small magnitude, 4 mmHg *(52)*. A Canadian study of 2224 children also found an association between CRP and SBP, in boys and girls, but the effect was not independent of body mass index (BMI) *(53)*. Similarly, a smaller study of 325 Columbian school-age children found that CRP was linearly associated with adiposity but not independently associated with blood pressure *(54)*. It may be that CRP is not directly associated with hypertension or that the effect may be of insufficient magnitude to be detected in children.

Unfortunately, there are currently no available medications that directly act upon the production or biological activity of CRP. Several classes of medications have been found to lower CRP, including statins *(55)*, fibrates *(56)*, nicotinic acid *(57)*, thiazolidinediones *(58)*, and angiotensin receptor blockers *(59)*. These drugs, used to mitigate CV risk factors, may exert some of their effects secondarily through reduction of CRP or a lower CRP may be an unrelated side effect. All of these classes of drugs would also be expected to have impact on

blood pressure for reasons other than reduction of CRP. Consequently, a clinical trial with one or more of these medications would be unlikely to resolve the mechanistic question of whether CRP is a cause or risk factor for hypertension.

OTHER INFLAMMATORY CYTOKINES AND CARDIOVASCULAR DISEASE

Several inflammatory markers, other than CRP, have been implicated in CV disease and hypertension. These include a reported association between serum IL-6 and IL-10 levels and CV risk *(60)*, and an association between TNF-α receptor polymorphisms and hypertension risk *(61)*; but the greatest amount of focus is on monocyte chemoattractant protein-1 (MCP-1). MCP-1 is a potent recruitment molecule specific for monocytes that has been implicated in atherosclerosis and hypertension. Produced by cytokine-activated vascular endothelial cells *(62)*, MCP-1 causes migration of monocytes into vascular intima initiating a perivascular inflammatory cycle that can lead to atherosclerotic plaque formation *(63)* and/or vascular smooth muscle cell proliferation and arteriolosclerosis *(64)*. Genetically engineered mice lacking the receptor for MCP-1 have significantly reduced atherosclerotic plaque formation *(63)*. CRP *(47)*, LDL-cholesterol *(65)*, and uric acid can activate endothelial MCP-1 expression in cultured cells; thus, it is hypothesized that MCP-1 *(66)* may modulate several pathways leading to increased cardiovascular risk. In a cross-sectional study of 263 adults, serum MCP-1 levels correlated with coronary risk factors including hypertension, hypercholesterolemia, diabetes, and obesity *(67)*. Single gene polymorphisms in the MCP-1 gene have also been linked to hypertension and ischemic heart disease *(68)*, but whether MCP-1 has a direct role in hypertension and CV disease remains an open question.

URIC ACID IN CHILDHOOD HYPERTENSION

The concept that uric acid may be involved in hypertension is not new. In the 1870s, Frederick Mahomed noted that many hypertensive patients came from gouty families and hypothesized that uric acid might be integral to the development of essential hypertension *(69)*. Ten years later, Haig *(70)* proposed that hyperuricemia was the underlying cause of many pathological conditions, including hypertension, diabetes, and 'rheumatism', and that low purine diets were a critical preventive measure. In 1909, Henri Huchard noted that renal arteriolosclerosis (the histological lesion of hypertension) was observed in three groups; those with gout, lead poisoning, or have a diet consisting mainly of fatty meats, all of which are associated with hyperuricemia *(71)*. Although an association between serum uric acid level and hypertension was repeatedly reported between 1950s and 1980s *(72–74)*, the lack of a plausible mechanism led it being largely ignored in medical practice.

In the last decade, new epidemiologic studies have rekindled an interest in the link between uric acid and hypertension (see Table 1). Three longitudinal Japanese studies showed an association between serum uric acid level and incident hypertension. Nakanishi et al. *(75)* showed a 1.6-fold increased risk of new hypertension over 6 years in young adult office works with serum uric acid level in the highest tertile. Taniguchi et al. *(76)* showed a twofold increased risk of new hypertension over 10 years associated with elevated uric acid in the Osaka Health Study. Masuo et al. *(77)* evaluated the linear association of serum uric acid level and systolic blood pressure, finding an average increase of 27 mmHg per 1 mg/dL increase in serum uric acid levels among nonobese young men. 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

Table 1
Epidemiology of Hyperuricemia and Hypertension

Study	*Year*	*Population*	*Finding*	*References*
Israeli Heart Study	1972	10,000 men	High uric acid associated with twofold risk of hypertension at 5 years	*(107)*
Fessel et al.	1973	348 adults	High uric acid associated with greater increase in SBP over 4 years	*(108)*
Gruskin	1985	55 adolescents	Mean uric acid higher in hypertensive children	*(90)*
Brand et al.	1985	4,286 adults	Uric acid had linear association with change in SBP over 9 years	*(74)*
Moscow Children's	1985	145 children	9% Normotensive and 73% hypertensive had uric acid >8 mg/dL	*(109)*
Hungarian Children's	1990	17,634 children	Uric acid predicts hypertension in late adolescence	*(89)*
Kaiser Permanente	1990	2,062 adults	High uric acid associated with twofold risk of hypertension at 6 years	*(110)*
University of Utah	1991	1,482 adults	High uric acid associated with twofold risk of hypertension over 7 years	*(111)*
NHANES	1993	6,768 children	High uric acid predicts hypertension in boys aged 12–17 years	*(112)*
Olivetti Heart Study	1994	619 men	High uric acid associated with twofold risk of hypertension at 12 years	*(113)*

Table 1
(continued)

Study	*Year*	*Population*	*Finding*	*References*
CARDIA Study	1999	5,115 men	High uric acid associated with increased hypertension in blacks	*(114)*
Osaka Health	2001	6,356 men	High uric acid associated with twofold risk of hypertension at 10 years	*(76)*
Hawaii LA Hiroshima	2001	140 men	High uric acid associated with 3.5-fold risk of hypertension at 15 years	*(115)*
Feig and Johnson	2003	125 children	Uric acid >5.5 mg/dL had 89% PPV for essential hypertension	*(91)*
Osaka Factory	2003	433 men	Each 1 mg/dL uric acid associate with 27 mmHg rise in SBP	*(77)*
Osaka Health II	2003	2,310 men	High uric acid associated with 1.6-fold risk of hypertension at 6 years	*(75)*
Okinawa	2004	4,489 adults	High uric acid associated with 1.7-fold risk of hypertension at 13 years	*(116)*
Bogalusa	2005	679 children	High uric acid associate with diastolic hypertension at 10 years	*(78)*
Framingham	2005	3,329 adults	High uric acid associated with 1.6-fold risk of hypertension at 4 years	*(79)*

Table 1
(continued)

Study	*Year*	*Population*	*Finding*	*References*
Normative Aging	2006	2,062 men	High uric acid associated with 1.5-fold risk of hypertension at 21 years	*(117)*
MRFIT	2006	3,073 men	High uric acid associated with 1.8-fold risk of hypertension at 6 years	*(118)*
ARIC	2006	9,104 adults	High uric acid associated with 1.5-fold risk of hypertension at 9 years	*(119)*
Beaver Dam	2006	2,520 adults	High uric acid associated with 1.7-fold risk of hypertension at 10 years	*(120)*
Health Professionals	2006	750 elderly men	High uric acid associated with 1.1-fold risk of hypertension at 8 years	*(121)*
CARDIA	2007	2,611 adults	Change in uric acid predicts change in blood pressure in young adults over 10 years	*(122)*
Women's Health	2009	1,469 women	High uric acid associated with 1.9-fold risk of hypertension	*(123)*
Jones et al.	2009	104 children	High uric acid associated with 2.1-fold risk of ABPM diastolic hypertension	*(124)*

in blood pressure within the normal range *(78)*. 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 *(79)*. Studies specifically of older and elderly patients have had variable results *(80–83)*, implying that if uric acid leads to hypertension, there may be a preferential effect in the young.

A rat model developed in the late 1990s provided a hypothetical mechanism for uric acid-mediated hypertension and significantly increased interest in this field *(84)*. The model requires that rats be fed an inhibitor of urate oxidase, oxonic acid, to increase their uric acid levels to those found in humans. Over 7 weeks of such treatment, systolic blood pressures increase an average of 22 mmHg. The increase in blood pressure can be prevented by the co-administration of the xanthine oxidase inhibitor allopurinol or by the uricosuric agent benziodarone, indicating that the rise in uric acid is the cause of the increased blood

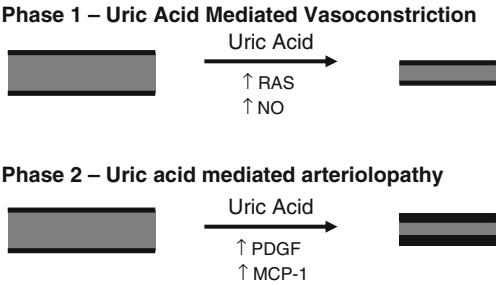

Fig. 1. Two phases of hyperuricemic hypertension: Animal model data suggest that hyperuricemia leads to hypertension in a step fashion. This is a schematic of the effects of uric acid on the blood vessels. The first phase is directly uric acid dependent and sodium independent. It occurs through the uric acid-mediated activation of the renin–angiotensin system and downregulation of endothelial nitric oxide, leading to a vasoconstricted state. The second phase, which develops over time, becomes sodium sensitive and uric acid independent. It occurs through the uric acid-mediated development of renal afferent arteriolosclerosis that induces an irreversible shift in the pressure natriuresis curve.

pressure *(84)*. After 7 weeks on a low salt diet, if the urate oxidase inhibitor, oxonic acid, is removed, the serum uric acid level decreases to normal as does the blood pressure over 3 weeks; however, if the hyperuricemic rats are then fed a high salt diet, they become hypertensive long term, even if hyperuricemia resolves *(85)*. The mechanism by which uric acid induces this change is complex and has been elucidated. Uric acid enters vascular smooth muscle cells through several biochemical steps and induces the production and elaboration of MCP-1 and platelet-derived growth factor (PDGF) *(66,84,86,87)*. This results in vascular smooth muscle proliferation and the thickening of arteriolar walls and the development of arteriolosclerosis (Fig. 1).

The two-phase development of hypertension in the rat model (phase 1, with high uric acid, and phase 2, with salt loading) provides a potential explanation for greater correlation between uric acid and hypertension in younger and prehypertensive populations. If humans follow a similar pattern, older patients would be expected to hypertension unrelated to uric acid levels. Thus, determining whether uric acid causes hypertension and to what extent, hyperuricemia ought to be managed should be approached in younger patients. Current data support this approach. In adolescents there is a close association between elevated serum uric acid level and the onset of essential hypertension. The Moscow Children's Hypertension Study reported hyperuricemia (>8.0 mg/dL) in 9.5% of children with normal blood pressure, 49% of children with borderline hypertension, and 73% of children with moderate and severe hypertension *(88)*. The Hungarian Children's Health Study followed all 17,624 children born in Budapest in 1964 for 13 years and observed elevated heart rate, early sexual maturity, and hyperuricemia were significantly associated with development of hypertension *(89)*. These two studies do not separate the hypertensive children by underlying diagnosis, so the relationship between serum uric acid level and hypertension may be skewed by ascertainment bias. In a small study, Gruskin *(90)* 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 levels (mean >6.5 mg/dL) and higher peripheral renin activity. In a racially diverse population referred for the evaluation of hypertension, Feig and Johnson *(91)* observed that the mean serum uric acid level in children with white coat hypertension was 3.6 mg/dL, slightly

higher in secondary hypertension (4.3 mg/dL) and significantly elevated in children with primary hypertension (6.7 mg/dL—tight, linear correlation between the serum uric acid levels and the systolic and diastolic blood pressures, r=0.8 for SBP and r=0.6 for DBP). Among patients referred for evaluation of hypertension, a serum uric acid level >5.5 mg/dL had an 89% positive predictive value for essential hypertension.

Results from a small very small, unblinded pilot study in children suggest that uric acid may directly contribute to the onset of hypertension in some humans. Five children, aged 14–17 years, with newly diagnosed and as yet untreated essential hypertension were treated for 1 month with allopurinol as a solitary pharmacological agent; all had a decrease in blood pressure by both casual and ambulatory monitoring and four of the five were normotensive at the end of 1 month. All also had a rebound in their blood pressures after discontinuation of the therapy *(92)*. A sample of 30 adolescents with newly diagnosed essential hypertension were treated in a randomized, double-blinded cross-over trial with allopurinol versus placebo. Sixty-seven percent of children while on allopurinol, and 91% of children who has serum uric acid level <5.5 mg/dL on treatment, had normal blood pressure, compared to 3% when children were on placebo *(93)*. While these observations should be confirmed in larger and more general population, if serum uric acid is indeed directly causing renal arteriolopathy, altered regulation of natriuresis and persistent systemic hypertension, it is a modifiable risk factor for CKD in the absence of other mechanisms.

HYPERURICEMIA ETIOLOGY

The causes of mild to moderate hyperuricemia in the young are not well established. In older patients, a variety of mechanisms, including decreased renal function, have been shown to lead to hyperuricemia. There are numerous medications that impair renal clearance of uric acid including loop and thiazide diuretics *(94)*. Genetic polymorphisms in anion transporters such as uric acid anion transporter-1 (URAT-1) may also lead to hyperuricemia *(95)*. Approximately 15% of uric acid clearance is through the GI tract, consequently small bowel disease or altered phenotype can also contribute *(96)*. Diets rich in fatty meats, seafood, and alcohol increase serum uric acid levels *(97,98)* and obesity confers a threefold increased risk of hyperuricemia *(99)*. Finally, as uric acid is the end point 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 levels *(100)*.

Serum uric acid levels throughout the population correlate with the rise in the obesity *(91)*, and since the introduction of high fructose corn syrup (HFCS) in the early 1970s, the intake of sweetener has increased *(101)*. Fructose increases uric acid, and it does so rapidly through activation of the fructokinase pathway in hepatocytes *(102)*. Fructokinase consumes ATP leading to an increased load of intracellular purines requiring metabolism and disposal through xanthine oxidase-mediated metabolism ending in uric acid *(102)*. Fructose-fed rats develop features of metabolic syndrome, hyperuricemia, and hypertension *(103)*, including the development of preglomerular arteriolopathy. Lowering uric acid prevents these changes despite ongoing fructose consumption *(101)*. Human studies also show that fructose loading leads to increase serum uric acid levels acutely, and that chronic increases fructose consumption leads to chronically increased serum uric acid and increases in blood pressure *(104,105)*. With the nearly universal exposure to sweetened foods and beverages in the pediatric population, it is very likely that much of the hyperuricemia, especially that associated with obesity, is dietary rather than genetic in origin *(106)*. What has

not yet been proven is whether active reduction of sweetener consumption is an effective way to reduce serum uric acid levels and or blood pressure.

CONCLUSIONS AND FURTHER DIRECTIONS

The common physiological thread among the potential mediators of hypertension discussed in this chapter is the induction of an inflammatory cascade. Endothelial dysfunction, perivascular infiltration of inflammatory cells, smooth muscle proliferation, and the development of renal afferent arteriolosclerosis likely represent a common pathway to hypertension that can be engaged by a variety of stimuli (see Fig. 2). If future studies bear out some or all of these mediators as important causes of hypertension, the potential therapies may be specific to specific mediators.

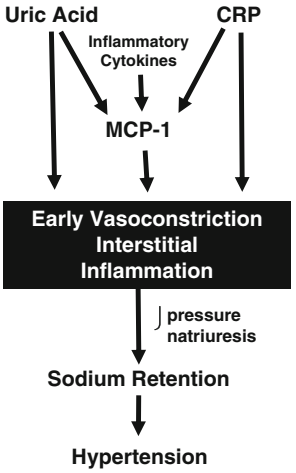

Fig. 2. A hypothetical common pathway for the development of hypertension secondary to inflammatory mediators, CRP, MCP-1 and uric acid.

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6 Monogenic and Polygenic Genetic Contributions to Hypertension

Julie R. Ingelfinger, MD

Contents

INTRODUCTION

More than 9 years have elapsed since the publications in February 2001 that provided the first maps of the human genome *(1,2)*. Increasingly, the identification of a specific gene—or genes—that causes a given disease is feasible. Indeed, genes involved in several rare, monogenic forms of familial hypertension have been identified. However, while the identification of a gene associated with Mendelian forms of hypertension is feasible, such an approach does not work as effectively for non-Mendelian forms of high blood pressure (BP), which have multiple genetic determinants. Many recently developed tools are available to reveal genes involved in primary hypertension, and studies have identified many associations with primary or essential hypertension, which is widely viewed as a polygenic disorder. This chapter discusses both monogenic and polygenic aspects of hypertension.

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") *(3–5)*. In this approach large kindreds with many affected family members are phenotyped, and the mode of inheritance—autosomal recessive, autosomal dominant, sex-linked, codominant, determined. Subsequently, linkage analysis is performed using highly polymorphic genetic markers such as

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_6
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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 logarithm of the odds (LOD) 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 commences. A search using additional highly polymorphic markers may also narrow the area of interest, leading to sequences of possible genes within the area.

Most monogenic forms of hypertension identified to date are due to gain-of-function mutations *(6,7)*, most of which result in overproduction of mineralocorticoids or increased mineralocorticoid activity. Severe hypertension, often from early life—even infancy—is not unusual. Clinical hallmarks include apparent volume expansion and suppressed plasma renin activity with variable hypokalemia. An approach to evaluation of those forms of hypertension associated with hypokalemia and suppressed renin activity is shown in Fig. 1 *(8)*.

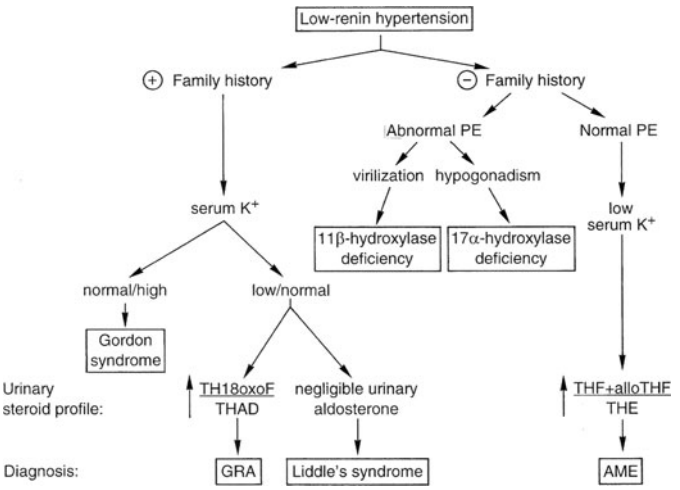

Fig. 1. Algorithm for evaluating children with low-renin hypertension. Several hypertensive syndromes share, as a common feature, very low plasma renin activity (PRA). These disorders are inherited as either an autosomal dominant (positive family history) or an autosomal recessive (negative family history) trait. Children with any of three syndromes, GRA, Liddle's syndrome, apparent mineralocorticoid excess (AME), share a clinical phenotype characterized by normal physical examinations (PEs), low PRA, and hypokalemia. These disorders are distinguishable from one another on the basis of characteristic urinary steroid profiles and genetic testing. K^+, Potassium; TH18oxoF/THAD ratio of urinary 18-oxo-tetrahydrocortisol (THAD) (normal 0–0.4, GRA patients > 1); THF+ alloTHF/THE ratio of the combined urinary tetrahydrocortisol (THF) and allotetrahydrocortisol (alloTHF) to urinary tetrahydrocortisone (THE) (normal < 1.3, AME patients five- to tenfold higher; from *(8)*).

Gain-of-function mutations in transporters in the distal nephrons of the renal tubules result in hypertension via salt and water retention by the kidney *(9)*. (While mutations and polymorphisms in the genes of various components of the renin–angiotensin–aldosterone system may lead to excessive renal sodium retention, no single RAS polymorphism causes

monogenic hypertension.) Clinically, most monogenic hypertension can be divided into those mutations that lead to overproduction of mineralocorticoids or increased mineralocorticoid activity and those that result in abnormalities of electrolyte transport, focusing on the role of the kidney in hypertension (Table 1) *(7)*. Additionally, some mutations in proto-oncogenes and genes that involve response to hypoxia have been linked to chromaffin tumors (Table 2) *(10)*.

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 *(11–15)*. GRA has been recognized since the 1960s, when Sutherland et al. *(16)* and New and Peterson *(17)* 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 11β-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 *(18,19)*. 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 *(20–22)*, 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 can be measured with a commercially available urinary steroid profile (Quest Diagnostics/Nichols Institute, San Juan Capistrano, CA) and will distinguish patients with GRA from others with AME or Liddle's syndrome *(23)*. 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 *(24,25)*. Dluhy et al. *(24)* 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 channel (ENaC) antagonists was sufficient to control BP in half of the hypertensive children, though the others required polypharmacy, and three had uncontrollable hypertension *(24)*.

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 *(6,7,18)*.

Familial Hyperaldosteronism Type 2 (OMIM #605635)

Familial hyperaldosteronism type 2, which appears to be autosomal dominant, is distinct from type 1 and is associated with hyperplasia of the adrenal cortex, an adenoma producing

Table 1
Forms of Monogenic Hypertension

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, ⇑ corticosterone (B), and DOC in plasma; serum androgens and estrogens very low; serum gonadotrophins very high	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 pseudohermaphroditism; female external genital phenotype in males; primary amenorrhea in females
Hyperaldosteronism				
Primary aldosteronism	⇓ PRA; cplasma aldosterone, 18-OH- and 18oxoF; 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

Table 1
(continued)

Signs and Sx	*Hormonal findings*	*Source*	*Genetics*	*Comment*
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) Familial hyperaldosteronism type 1	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
Familial hyperaldosteronism type 2	Hyperaldosteronism. Not suppressed by dexamethasone		Unknown. A 5-Mb locus on chromosome 7p22 appears implicated	
Apparent mineralocorticoid excess (AME)	⇑ plasma ACTH and secretory rates of all corticosteroids; nl serum F (delayed plasma clearance)	⇑ plasma F bioact. in periphery (F-F→E) of bi-dir. 11β-OHSD or slow clearance by 5-α/β reduction to allo dihydro-F	Type 2 11β-OHSD mutations	Cardiac conduction changes; LVH, vessel remodeling; some calcium abnormalities; nephrocalcinosis; rickets
Mineralocorticoid receptor gain-of-function mutation	Low-renin, low-aldosterone, hypokalemia	Mineralocorticoid receptor remains active	Missense mutation—serine at amino acid 810 in the mineralocorticoid receptor is changed to leucine (S810L)	

Table 1
(continued)

Signs and Sx	*Hormonal findings*	*Source*	*Genetics*	*Comment*
Nonsteroidal defects				
Liddle's 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
Brachydactyly and hypertension	No specific biochemical findings	Not a disorder of steroidogenesis	Inversion, deletion, and reinsertion at 12p12.2 to p11.2	Brachydactyly and hypertension

Adapted and expanded from New MI, Crawford C, Virdis R. Low Renin Hypertension in Childhood, in Lifshitz F (Ed.) Pediatric Endocrinology, Third Edition, Ch 53, p. 776.

Table 2
Hereditary Syndromes Associated with Pheochromocytoma

Syndrome	Clinical phenotype	Risk of Pheochromocytoma	Mutated Germ-line gene
		%	
MEN-2A	Medullary carcinoma of the thyroid, hyperparathyroidism	50	*RET* (proto-oncogene)
MEN-2B	Medullary carcinoma of the thyroid, multiple mucosal neuromas, marfanoid habitus, hyperparathyroidism	50	*RET* (proto-oncogene)
Neurofibromatosis type 1	Neurofibromas of peripheral nerves, cafe au lait spots	1	*NF1*
Von Hippel–Lindau disease (retinal cerebellar hemangioblastosis)	Retinal angioma, CNS hemangioblastoma, renal-cell carcinoma, pencreatic and renal cysts	10–20	*VHL*
Familial paraganglioma syndrome	Carotid-body tumor (chemodectoma)	20 (estimated)	*SDHS, SDHB*

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, the gene for the succinate dehydrogenase subunit B.

With permission from *(10)*.

aldosterone, or both *(26–29)*. It has been estimated to be fivefold more common than GRA *(29)*. Dexamethasone fails to suppress the findings. To date, no mutation has been identified, though linkage studies have identified a 5-Mb locus on chromosome 7p22. Recently, Stowasser group *(29)* examined a number of candidate genes within 7p22, many of which involve cell growth, but have not yet definitively identified the gene responsible.

Apparent Mineralocorticoid Excess (OMIM # 218030)

Low-renin hypertension, often severe and accompanied by hypokalemia and metabolic alkalosis *(30)*, is the hallmark of apparent mineralocorticoid excess (AME), first described in 1977 by New et al. *(31,32)*. 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 keto-metabolites. 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 *(31,32)*, whereas 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. A high cortisol:cortisone ratio in plasma or an abnormal urinary ratio of tetrahydrocortisol/tetrahydrocortisone (THF/THE), in which THF predominates, makes the diagnosis.

Affected children are at high risk for cardiovascular complications, and some develop nephrocalcinosis and renal failure *(33)*; early therapy may lead to better outcome.

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 *(34,35)*; a coactivator defect with resistance to multiple steroids *(36)*; and hypertension without the characteristic

findings of AME in a heterozygous father and homozygous daughter who have mutations in 11β-HSD2 *(37)*. A recent paper reported a Brazilian child with a homozygous missense mutation p.R186C in the *HSD11B2* gene *(38)*.

The hypertension in AME appears renally mediated, but recent evidence suggests that ultimately, the disorder changes from increased sodium resorption to a vascular form of hypertension *(39)*.

Mineralocorticoid Receptor Gain-of-Function Mutation

A form of monogenic hypertension due to a gain-of-function mutation in the mineralocorticoid receptor occurs due to a missense mutation that was first found in a teenage boy with hypertension, low-renin and aldosterone levels, as well as mild hypokalemia *(40)*. In toto, 11 persons in his family had this mutation. In this 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 *(41,42)*. Early death due to heart failure occurred in the index family *(40)*.

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 *(43)*.

Steroidogenic Enzyme Defects Leading to Hypertension

Rare autosomal recessive defects in steroidogenesis associated with hypertension were well recognized before the genomic era. Cortisol is normally synthesized under the control of ACTH in the zona fasciculata, whereas 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.

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 *(44–46)*. Any enzyme in the pathways of steroidogenesis may contain a mutation; the most commonly affected is 21-hydroxylase. However, mutations in 21-hydroxylase are not 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 *(44–50)*, 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 *(44–50)*. 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 for 11β-hydroxylase deficiency should focus on normalizing steroids. Administered glucocorticoids should normalize cortisol and reduce ACTH secretion and levels to normal, thus stopping oversecretion of deoxycorticosterone (DOC). Hypertension generally resolves with such therapy *(45)*. When hypertension is severe, antihypertensive therapy should be instituted until the BP is controlled; such therapy can be tapered later.

Additional mutations can cause this syndrome. For example, a patient with 11β-hydroxylation inhibition for 17-α-hydroxylated steroids but with intact 17-deoxysteroid hydroxylation has been reported *(50)*. Multiple mutations affecting the *CYP11B1* gene have been described; these include frameshifts, point mutations, extra triplet repeats, and stop mutations *(30, 51–54)*.

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 *(55–58)*. 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 *(57)*. 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 control BP.

Mutations in Renal Transporters Causing Low-Renin Hypertension

Pseudohypoaldosteronism Type II—Gordon's Syndrome (OMIM#145260)

Pseudohypoaldosteronism type II (also known as Gordon's 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 WNK4 kinase family *(59–63)*. 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 *(63)*. Aldosterone receptor antagonists do not correct the observed abnormalities.

PHAII genes have been mapped to chromosomes 17, 1, and 12 *(59,60)*. 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 WNK1 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's Syndrome (OMIM # 177200)

In 1963 Liddle et al. *(64)* described 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 hypertension, but those of the mineralocorticoid receptor did not. A general abnormality in sodium transport seemed apparent, as the red blood cell transport systems were not normal *(65)*. A major abnormality in renal salt handling seemed likely when a patient with Liddle's syndrome underwent a renal transplant, and hypertension and hypokalemia resolved post-transplant *(66)*.

While the clinical picture of Liddle's syndrome is one of aldosterone excess, aldosterone and renin levels are very low *(8)*. Hypokalemia is not invariably present. A defect in renal sodium transport is now known to cause Liddle's 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 β and γ subunits of the ENaC have been identified (both lie on chromosome 16) *(67,68)*. Thus, the defect in Liddle's syndrome leads to constitutive activation of amiloride-sensitive epithelial sodium channels (ENaCs) in distal renal tubules, causing excess sodium reabsorption. Additionally, these gain-of-function mutations prolong the half-life of ENaCs at the renal distal tubule apical cell surface, resulting in increased channel number *(69)*.

Pheochromocytoma-Predisposing Syndromes

A variety of *RET* proto-oncogene mutations and abnormalities in tumor suppressor genes are associated with autosomal dominant inheritance of pheochromocytomas, as summarized in Table 2 *(10,70–75)*. A number of paraganglioma and pheochromocytoma susceptibility genes inherited in an autosomal dominant pattern appear to convey a propensity toward developing such tumors *(10)*. Both glomus tumors and pheochromocytomas are derived from neural-crest tissues, and the genes identified in one type of tumor may appear in the other *(76)*. For instance, germ-line mutations have been reported both in families with autosomal dominant glomus tumors and in registries with sporadic cases of pheochromocytoma *(77)*. In addition, other pheochromocytoma-susceptibility genes include the proto-oncogene *RET* (multiple endocrine neoplasia syndrome type 2 (MEN-2)), the tumor suppressor gene *VHL* observed in families with von Hippel–Lindau syndrome, 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 *(78–80)*. In von Hippel–Lindau disease, inactivating (loss-of-function) mutations are present 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 appears that apparently sporadic chromaffin tumors may also contain mutations in these genes.

Hypertension with Brachydactyly (OMIM #112410)

Hypertension with brachydactyly, also called brachydactyly, type E, with short stature and hypertension (Bilginturan syndrome) was first described in 1973 in a Turkish kindred *(81)*. 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 *(82,83)*.

Patients with this form of hypertension have normal sympathetic nervous system and renin–angiotensin system responses. In 1996, some abnormal arterial loops were observed 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 *(84)*. Another family, in Japan, also had similar findings, and a deletion in 12p was reported in that family *(85)*.

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 *(86)*). 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 PPARγ *(87)* There has also been a description of hypertension, hypomagnesemia, and hypercholesterolemia due to an abnormality in mitochondrial tRNA. In this case, impaired ribosomal binding is due to a missense mutation in the mitochondrial tRNA *(88)*.

When to Suspect Monogenic Hypertension

Table 3 lists the situations in which the astute clinician should consider monogenic hypertension *(7)*. These include both clinical and laboratory findings that should point toward further evaluation. Significant among these are a strong family history of hyper-

Table 3
When to Suspect a Hypertensive Genetic Disorder

At-risk members of kindreds with a known monogenic hypertensive disorder (e.g., multiple endocrine neoplasia, syndromes)
Hypokalemia in hypertensive children and their first-degree relatives
Juvenile onset of hypertension, particularly if plasma renin is suppressed
Physical findings suggestive of syndromes or hypertensive disorders (e.g., retinal angiomas, neck mass, hyperparathyroidism in patient with a pheochromocytoma)

Adapted from *(7)*.

tension, particularly when the BP is difficult to control within the family. Low plasma renin activity should also point toward the possibility that a defined form of hypertension may be present.

NON-MENDELIAN, POLYGENIC HYPERTENSION

The genetic contribution to a widely prevalent condition such as essential (primary) hypertension is generally considered to involve multiple genes and is thus termed polygenic. The possibility for determining the genes 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 is described in the following sections.

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. In the 1980s, it was estimated that 5–10 genes control BP *(89)*. In 2000, Rapp *(90)* summarized available research and estimated that 24 chromosomal regions in 19 chromosomes were associated with hypertension in various rat strains. A recent review by Delles et al. *(91)* 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 *(92)*.

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-α, the bradykinin receptor, and the angiotensin type 2 receptor, as well as other members of the renin–angiotensin system *(93)*.

Genetic manipulation in mice has been successful in exploring contributions of various candidate genes (reviewed in *(94)*), most notably those of the renin–angiotensin system through two approaches, overexpression of a given gene (with "transgenic" animals *(90)*) and deleting gene function (with "knockouts"). An additional approach is to use gene targeting in embryonic stem (ES) cell cultures *(95–97)*.

Inbred strains rather than transgenic or knockouts have led to important findings *(97–100)*. A number of studies, notably those of Jacob et al. *(97)* and Hilbert et al. *(98)*, 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 *(91,99)*.

Human Hypertension

A variety of studies have pointed to a link between human hypertension and genes of the renin–angiotensin system (summarized in *(101,102)*). 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(s) that is 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 *(103–118)*.

Linkage analysis may still be an initial step *(3–5)*, but it is not as powerful a tool 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. 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 *(3–5)*. An 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 through linkage disequilibrium or association testing between disease and genetic markers, often with single-nucleotide polymorphisms (SNPs). SNPs occur roughly every 1000 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 *(110,111)*.

Genome-wide screens of the human genome aiming to discover hypertension genes have suggested many loci of interest *(112,113)*. These 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 2000 sib pairs from 1500 or so families *(112)*. Using genomic scan data from four partner networks, the US Family Blood Pressure Program (FBPP) *(113)* 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 sib pairs *(109)* and Finnish twins *(104)*, as well as a discordant sib-pair screen. Recently Caulfield et al. *(114)* phenotyped 2010 sib pairs drawn from 1599 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. Their linkage analysis identified a locus on chromosome 6q with an 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 *(114)*. One of these loci was the same as that found in the Chinese and Finnish studies *(114)*.

Within the last few years, there have been further genome-wide association studies (GWAS) concerning hypertension reported *(119,120)*. In 2007 Levy et al. *(121)* 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 gene. 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 *(122)*. 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^{2+} transporting, plasma membrane 1 (*ATP2B*) gene *(123)*. These rather disappointing results from GWAS studies on hypertension are discussed to indicate the complexity of primary hypertension.

Two consortiums have lately 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 8 regions that reached genome-wide significance. These regions were associated with hypertension and lie in close proximity to genes *CYP17A1*, *CYP1A2*, *FGF5*, *SH2B3*, *MTHFR*, *ZNF652*, and *PLCD3* and to the chromosome 10 open-reading frame 107 (c10orf107) *(124)*. Further, the so-called CHARGE consortium *(125)* 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 and 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 *(124)*. 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, β2 subunit) *(124)*.

Candidate Genes

Another approach in assessing polygenic hypertension is to use candidate genes—which 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 *(114)*, 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 on 9q 9q and GPR21 on 9q33; and on 2q24.1 there is a potassium channel, KCNJ3.

Microarrays are used to identify differential expression of expressed sequences in tissues from affected and unaffected persons. These 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 renin–angiotensin system. 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 renin–angiotensin system, but many other genes. For example, Izawa et al. *(117)* 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 1940 persons. They found that polymorphisms in the CC chemokine receptor 2 gene were associated with hypertension in men and those in the *TNF-α* gene with hypertension in women *(117)*. In a GWAS in African-Americans, Adeyemo et al. *(126)* 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 by 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 are 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.

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

7 Casual Blood Pressure Methodology

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Contents

HISTORICAL BACKGROUND

The concept of measuring blood pressure (BP) has significantly evolved over the past two centuries, overcoming the challenge posed by the well-established, but clearly subjective, art of palpation of the pulse for 'measures' other than simply determining heart rate. In the United States, the BP cuff was introduced by Cushing in Baltimore in 1901 and in Boston in 1903 *(1,2)* when he returned from a trip to Italy with a version of a Riva-Rocci mercury sphygmomanometer. Recognizing the obstacles to be overcome, Cushing noted, "The belief is more or less prevalent that the powers of observation so markedly developed in our predecessors have, to a large extent, become blunted in us, owing to the employment of instrumental aids to exactness, and the art of medicine consequently has always adopted them with considerable reluctance" *(2)*.

Cook and Briggs *(3)*, two resident house officers, quickly introduced the new cuff into clinical practice at the Johns Hopkins Hospital. They apparently had a single-sized rubber bladder covered by a canvas case that was fitted with hook and eye attachments so that it could be "fitted to any arm from that of an infant to that of a large adult". Interestingly, despite the one-size fits-all bladder, they felt that arm size was a 'very small factor' in obtaining the pressure using their device. They reported the first 'normal' values in children, systolics between 75 and 90 mmHg during the first 2 years of life and

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_7
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90–110 mmHg during early childhood. This compared with their reported normal systolic BP of 130 mmHg in young adult males and 115–120 mmHg in young women. In their extensive report, they demonstrated BP responses during surgery, shock, hemorrhage, postoperative recovery, obstetrics, hypertension, and sepsis. They also documented the response of BP to pressors and volume *(3)*. It should be noted that this early technique was based upon palpation of the brachial pulse.

At roughly the same time, Korotkoff was describing sounds that could be heard by placing a stethoscope over the brachial artery at the elbow below a BP cuff as the cuff pressure was slowly released [Korotkoff NC. On methods of studying blood pressure. Izvestiia Voennomeditsinskite Akademiia. 1905;11:365, as translated in *(4)*]. The original report by Korotkoff was in fact only one paragraph long, followed by a discussion. This auscultatory method was rapidly adopted, with data in adults from the United States reported in 1910 *(5)*. The value of BP determination was quickly recognized. By 1925 reports of the association between BP and mortality among US life insurance policyholders first appeared *(6)*. Despite this, coordinated studies of BP in children were slow to be developed. The Specialized Centers of Research—Atherosclerosis (SCOR-A) studies in Bogalusa, LA; Miami, FL; and Muscatine, IA were among the earliest, starting in the late 1960s and early 1970s *(6)*. These studies were all based on the auscultatory method.

IMPORTANCE OF BP MEASUREMENT

The critical need for a 'standard' methodology for BP measurement in children stems from the recognition that both high BP and frank hypertension are pervasive problems in the present era *(7)*. The Third National Health and Nutrition Examination Survey (NHANES) showed the prevalence of frank hypertension (BP > 140/90 mmHg) in adults in the United States to be as high as 25%, with an even higher prevalence of 'suboptimal' BP *(3,7)*. While the epidemiology of childhood hypertension is less well defined, the reported prevalence of pediatric hypertension varies from a low of 0.8% *(8)* to a high of 5% *(9)*. Notwithstanding the lower prevalence of hypertension in children, the clinical impact of BP monitoring in children should by no means be considered negligible. This is based on the premise that BP 'tracks' from childhood into adulthood, and that, with intervention, the long-term adverse consequences of hypertension are almost entirely preventable. Tracking, which will be addressed in a subsequent chapter in greater detail, is defined as the tendency of an individual to maintain his or her percentile rank for a given parameter with age. While there is ongoing controversy as to how predictive childhood BP, as measured by casual methods, is for adult hypertension, it certainly appears that children who might be expected to be at greatest risk of cardiovascular complications, that is, those with persistently elevated BP readings, high body mass index, excessive weight gain, and a family history of hypertension, especially in the older age groups, have higher coefficients of tracking of BP into adulthood, and are, therefore, more likely to remain hypertensive as adults *(10–12)*. Moreover, childhood BP remains, to date, the strongest identified predictor for adult hypertension *(13)*.

Extrapolating from the adult medical literature, it has long been believed that children with hypertension are at high risk of long-term morbidity and mortality. Clearly high BP, and even less than 'optimal' BP *(14)* in adults has been shown to be a risk factor for cardiovascular morbidity (heart failure and myocardial infarction) *(15,16)*, cerebrovascular events (stroke) *(17)*, and end-stage renal disease *(18)*. Not only that, studies both in adults *(19)*

and in children *(20)* have demonstrated that hypertension is an important marker since its presence is strongly associated with the coexistence of other metabolic abnormalities such as dyslipidemia, obesity, and insulin resistance, all of which compound the risk of cardiovascular and cerebrovascular morbidity. Even if one considers the link between childhood BP and adult hypertension suspect, the more short-term adverse effects of severe hypertension, which is often clinically silent, on organ function can lead to life-threatening complications such as aortic dissection *(21)*, intracranial hemorrhage, heart failure *(22)*, and encephalopathy *(23)*. Less devastating, but possibly an equally worrisome effect of hypertension, is left ventricular hypertrophy, a major risk factor in adults for morbid cardiac events *(24)*.

When one considers that hypertension is prevalent in epidemic proportions in adults, its origins can be traced back, at least to some extent, into childhood, and it is associated with adverse short- and long- term consequences, most of which, hypothetically, can be prevented with early detection and treatment, it should come as no surprise that the periodic measurement of BP and moreover, the accurate measurement of BP, is of critical importance. Recognizing the importance of BP monitoring, the National Heart, Lung and Blood Institute and the American Academy of Pediatrics have long advocated for the routine monitoring of BP in all children above the age of 3 years on an annual basis *(25)*, or at least at the time of routine examinations. Consequently BP measurements in children have become commonplace. However, at the same time, so has the number of different devices being employed for its measurement, causing confusion and lack of uniformity in the method of BP determination. This raises important questions regarding the validity and accuracy of these devices and also highlights the need for a standardized means of testing and monitoring their performance to avoid errors in measurement that could have egregious consequences. This is even more important, when one recognizes how much more common home BP monitoring has become, both for the diagnosis and management of hypertension.

Before we discuss the individual methods for causal BP measurement in children, let us clarify the term ‘casual’. The use of the term ‘casual’, in this chapter, refers to the more conventional practice of obtaining BP readings on an episodic or intermittent basis such as readings during an office visit, as opposed to the more ‘continuous’ technique of ambulatory BP monitoring, which is addressed in a more comprehensive manner in Chapter 10.

GENERAL ISSUES IN THE MEASUREMENT OF BP

There are certain general issues in the measurement of BP that apply both to children and to adults. These are discussed quite thoroughly in the American Heart Association Guidelines for the Measurement of BP *(26)* and in a review by Gillman and Cook *(27)*. Basically, these issues can be categorized into those that relate to the equipment, the patient, and the observer.

Equipment: Obviously, the equipment must be maintained, calibrated, and functional. All devices for measuring BP require ongoing maintenance. Even mercury columns can be inaccurate *(28)*.

Perhaps the most important source of error related to the equipment in the measuring process pertains to selection of the proper size cuff. This remains an area of controversy since most suggestions as to what constitutes an appropriate cuff size are based on much opinion and very limited evidence. The present viewpoint is that the ‘proper’ cuff is one in which the inflatable bladder either has a width that is at least 38% of the arm circumference

and/or a length that encircles at least 90% if not the entire upper arm *(27)*. Similarly, the 4th Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents recommends that the bladder of the cuff have a width that is approximately 40% of the arm circumference midway between the olecranon and the acromion; this corresponds to a cuff bladder that will cover 80–100% of the arm circumference *(25)*. The British have suggested that three cuffs with bladders measuring 4 × 13 cm, 10 ×18 cm, and the adult dimensions 12 × 26 cm are sufficient for the range of arm sizes likely to be encountered in children from 0 to 14 years of age *(29)*. This degree of standardization of commercially available cuffs is not the case in the United States. It is interesting to note that the British cuffs have width/length ratios that (1) are variable and (2) would not allow the combination of a width/arm circumference ratio of 0.4 at the same time that they allow a length/arm circumference ratio of 0.9–1.0. It is well established that undercuffing, that is, 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 large for the arm will underestimate true BP. Too large in this context generally implies widths that exceed the recommended 0.38–0.4 ratio to arm circumference. Overly long cuffs, which of necessity will overlap, do not seem to generate significant errors *(27,30)*.

The problem of cuff size selection is aggravated by the lack of standards in the United States. Although Association for the Advancement of Medical Instrumentation (AAMI) and AHA standards call for cuffs that allow a cuff width to arm circumference ratio of 0.4, and also call for a bladder length to arm circumference ratio of 0.8, they do not take the logical step of establishing a minimal bladder width to length ratio of 0.5. As a result of the lack of standards, there is a wide variability in commercially available cuffs that are designed for children. In a 1996 survey of BP cuff manufacturers by one of the authors (BZM), cuff sizes given names suggesting the population for which they were intended, were tabulated (see Table 1). The 4th Report did recommend standardization of BP cuff bladder sizes for children *(25)*.

Patient factors: Several issues relating to the patient are seemingly self-evident and therefore often overlooked. For a proper BP measurement, the subject should have sat calmly for 5 min, and not have used caffeine or tobacco products for at least 30 min (alcohol and food are also often included on this list). In addition, the use of vasoactive medications should be noted. In children this includes decongestants, while for adolescents nutritional supplements, some of which contain ephedrine or related compounds, should be kept in mind.

It has been established in adults and extrapolated to children that the proper position for the patient to be in during BP measurements is sitting with the back supported and the feet flat on the floor. Of course, for infants and toddlers, the supine posture, by necessity, is also appropriate *(27)*. The arm to be used should be elevated to heart level *(31)*. BPs also vary with time of day and ambient room temperature *(27)*.

Observer: There are many device/method-specific issues that relate to the observer. Suffice it to state that 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 determine if the patient issues listed above are in fact accounted for. The observer also needs to properly select the cuff and apply it to the upper arm. This includes making sure that the cuff is placed on the bare arm, and that no restricting clothes are placed above the cuff (e.g., a tightly rolled sleeve).

Table 1
Commercially Available BP Cuffs Available for Infants and Children in 1996

Company	*Cuff (W × L)*	*Bladder (W × L)*
	Newborn/Premature	
WA/TYCOS	5.3 × 18.8	
BAUM	4.5 × 23	2.5 × 5
SICOA	5.2 × 18	4 × 8
GRAHAM FIELD	5.2 × 18.5	4 × 8
KOSAN/BRESCO	5.5 × 20 (prem)	4 × 9
	4 × 15 (sm prem)	2.5 × 7
K-T-K	5 × 23	
	5 × 16	
RIESTER	5 × 15.5 (NB)	3 × 5
ERKA	4.5 × 25	2.5 × 15
CREST-PYMA		2.8 × 8.4
ACCOSON		2.5 × 10.2
	Infant	
WA/TYCOS	7.4 × 26.1	5.6 × 11.9
BAUM	8 × 29	6 × 12
SICOA	7.5 × 26	5.5 × 11.5
GRAHAM FIELD	7.5 × 26.1	5.5 × 11.5
PROPPER	7.6 × 25.4	5.7 × 11.4
WINMED	7.5 × 25.4	5.7 × 11.4
K-T-K	7 × 29	
RIESTER	7.2 × 23	5 × 8
ERKA	7 × 28	5.5 × 15
CREST-MABIS		6.4 × 12.1
CREST-PYMA		5.3 × 11.4
ACCOSON		5.1 × 10.2
	Child	
WA/TYCOS	10.4 × 35.3	8.6 × 17.8
BAUM	11 × 41	9 × 18
SICOA	10.5 × 34.2	8.5 × 17
SAMMONS-PRESTON		10.2 × 17.9
GRAHAM FIELD	10.5 × 34.2	8.5 × 17
PROPPER	10.8 × 34.3	8.9 × 17.5
KOSAN/BRESCO	11 × 35 (child)	9 × 18
	8 × 26 (peds)	6 × 12
	9.5 × 30 (sm Child)	7.5 × 15

Table 1
(continued)

Company	*Newborn/Premature Cuff (W × L)*	*Bladder (W × L)*
WINMED	11 × 33.5	7.6 × 17.7
K-T-K	11 × 40	
	9.5 × 33	
RIESTER	10 × 35.5	8 × 13
ERKA	9 × 39	8 × 20
CREST-MABIS		8.3 × 17.8
CREST-PYMA		7.9 × 15.2
ACCOSON		10.2 × 19.1
		7.6 × 15.2 (young)
		8.0 × 18.0 (new)
		4 × 13 (new sm)

There is a wide range of bladder sizes for each category. Bladders that do not have a length = twice the width are unlikely to meet AAMI and AHA criteria for a width to arm circumference ratio of 0.4, while encircling 80% of the upper arm. (Data reported to Bruce Morgenstern by the manufacturers, 1996.) Dimensions are in centimeters.

METHODS OF BP MEASUREMENT

Auscultatory Methods of BP Measurement

Both mercury and aneroid devices are subject to significant observer issues. Primarily of course, the observer must be able to hear and interpret the Korotkoff sounds accurately. This requires training, which is often accomplished with taped recordings of Korotkoff sounds or stethoscopes with two sets of earpieces. The correct performance of the auscultatory method requires that the systolic pressure first be approximated by palpation. The proper bleed rate is suggested to be 2 mmHg/s, something which is even more critical when the patient's pulse rate is slow *(31)*.

Although extensive data are lacking, extant data suggest that in children, as in adults, the auscultatory method be performed with the bell of a stethoscope. The proponents of the use of the bell feel that this helps to augment the Korotkoff sounds. This brings us to yet another area of controversy with auscultation-determining which Korotkoff sound, K4 or K5, represents the diastolic BP more accurately.

In the original report of the Task Force on Blood Pressure control in children *(32)*, K4 was accepted as the measure of diastolic BP for children less than 13 years of age. In the most recent report *(25)*, this was changed to K5, since data were available to report normal K5 values in younger children, and since this obviated the step in BP values that otherwise occurred at age 13 years. However, this recommendation has not been universally accepted *(33–35)*. One study, in fact, has suggested that K4 diastolic BP measured in childhood is a better predictor of adult hypertension *(36)*.

A final and critical observer issue is observer bias. At it is simplest, this occurs when the observer has a terminal digit preference, and tends to report many BP values ending in that number (e.g., if it is zero, the majority of reported systolics and diastolics will end in

zero). Also, there is the matter of whether K5, disappearance, is the last sound heard, or 2 mmHg below that value. More complex observer biases can occur when the observer has been informed of his or her digit preference and then overcompensates, avoiding reporting values with that digit. Finally, there is the bias introduced by the knowledge of a patient's previous values, described more fully in the section on random-zero sphygmomanometers (RZSs) below.

Conventional Mercury Sphygmomanometry

Mercury sphygmomanometry has been considered the 'gold standard' against which other noninvasive measures are compared. The process is straightforward, but not necessarily easy. The components of the system include the bladder and cuff, tubing, a bulb with a screw-controlled bleed valve, a mercury reservoir, and the manometer, which has a filter at the top. Regular maintenance of the tubing, the bulb, the mercury in the reservoir, and the manometer is necessary to maintain accuracy. If the filter atop the manometer becomes clogged, the mercury will not move well in the column *(28)*.

Despite its status as the gold standard, mercury manometers, when systematically evaluated, have a significant number of problems that may preclude accurate use, even if the observer and patient issues are overcome. In a study at the St George's Hospital Medical School in London, UK, of 444 devices studied, 167 (38%) had dirty columns. Ninety-five (21%) of these were due to oxidization of the mercury so that the calibration markings were obscured, making it difficult to read the level of the mercury column. In 81 (18%) the column containing the mercury had either been rotated or the markings on the columns were badly faded, again making it difficult to read the level of the mercury meniscus. In three, mercury had leaked into the metal box. One machine had so little mercury in the column that when it was inflated, air bubbled through the mercury in the column, yet it was still in use *(28)*.

In a number of other studies, between 12 and 21% of evaluated mercury sphygmomanometers were not accurate when tested, but they were still being used clinically *(37,38)*. In a systematic evaluation of sphygmomanometers in a health district in the UK, none of the 356 instruments tested met all of the standards compiled for the project (project standards) or all of the relevant British regulatory standards; 14 (39.3%) met less than half of the British standards. Only 220 (61.8%) instruments tested were accurate at all six pressure levels in a calibration check; 12 sphygmomanometers met the accuracy standard at only three pressure levels, while 13 were inaccurate at all pressure levels tested. The authors also developed health and safety standards for the use and handling of mercury manometers. Eighty-six percent of the devices studies did not meet all five health and safety related standards *(39)*.

It appears that mercury manometers are likely to be phased out over the next few years, not for reasons of inaccuracy or device failure, although these are not all that uncommon *(28)*, but more for environmental reasons. This process is already taking place to greater or lesser degree in Europe, and several states in the United States have passed regulations concerning the handling of mercury that make it far too expensive to use mercury manometers *(40)*. Although the American Heart Association has taken a position against the elimination of the mercury manometer, it remains to be seen if they can slow this movement *(41)*.

Aneroid Manometry

The aneroid manometer functions in the process of auscultatory BP measurement in essentially the same way as the mercury column. The system comprises of a metal bellows,

a mechanical amplifier, springs, and a gauge that displays the pressure in the cuff and tubing of the sphygmomanometer. Aneroid devices are often felt to be less accurate than mercury columns *(42,43)*.

Aneroid manometers were evaluated in many of the same studies cited for the assessment of mercury manometers. Mion and Pierin *(38)* demonstrated that 44% of devices in the hospital and 61% of devices in outpatient settings differed by more than 3 mmHg from the standard. In the Canadian study of Vanasse, 17.7% of aneroid manometers were off by $\geq$ 5 mmHg, and 15% had at least one malfunctioning component (but 52.3% of the mercury devices did) *(37)*. Knight et al. *(39)*, as part of the same systematic study in the UK described for mercury manometers, found that none of the aneroid instruments tested met all of the project standards or all of the British regulatory standards. Seven (6.1%) of 114 devices met fewer than half of the British regulatory standards. The authors combined 14 standards against which aneroid manometers were compared for accuracy. Twenty-nine (25%) of the instruments met all 14 standards and two (1.7%) met 7 or less *(39)*.

Additional data also demonstrate that aneroid devices can be inaccurate. In one study, using the very rigid standard of $\pm$3 mmHg concordance with the mercury standard, 35% of devices were considered 'intolerant' at two of five pressures measured *(44)*. In another assessment of accuracy, Jones et al. *(45)* found that 34% of devices were not accurate to within 4 mmHg, but only 10% were not accurate to within 8 mmHg. In a recent study, using 10 mmHg as the criteria for accuracy, 1% of mercury manometers and 10% of aneroid devices were deemed inaccurate *(46)*.

The underlying reason for this apparent inaccuracy of aneroid devices is likely the lack of a regular program of calibration and maintenance. When practitioners in Humberside and Yorkshire were surveyed in 1988, 23.5% of the 1223 respondents admitted to never servicing the sphygmomanometers in their practices over a mean of 5.75 years *(47)*. However, it has been established that with proper calibration, aneroid devices are quite accurate manometers, and therefore subject only to the errors inherent to the auscultatory method *(44,48)*. Accuracy rates with mean differences from a mercury standard of $\pm$0.2 mmHg have been reported *(49)*. In the Mayo Clinic experience, with a program of regular maintenance and calibration, more than 99% of actively used aneroid devices remain within 3 mmHg of a digital pressure gauge standard over 6 month periods *(48)*.

Random-Zero Sphygmomanometry

The RZS was devised in 1970 as a modification of Garrow's 'zero-muddler sphygmomanometer', in an attempt to eliminate observer biases related to terminal digit preference and to previous knowledge of recorded BPs, both of which are common during conventional sphygmomanometry *(50)*. Therefore it has been considered by many to be the 'gold standard' for epidemiological studies, and has been employed in studies such as the Multiple Risk Factor Intervention Trial (MRFIT) *(51)*, and the Hypertension Prevention Trial *(52)* in adults.

The machine works on the basic principle that each time a BP reading is obtained, the observer is 'blinded' to the reading until after the measurement has been completed. This comes about as a result of the incorporation of a mercury reservoir that fills randomly and to a variable degree during each inflation of the cuff, and adds a random amount of mercury to the manometer column. The amount of mercury added to the reservoir and to the column is unknown to the person using the machine until after the BP cuff has been deflated, at which point in time this 'random-zero' number can be read and subtracted from the uncorrected

systolic and diastolic readings. While experience with the RZS is more limited in children, at least one group of investigators has used it for the 'Study of Cardiovascular Risk in Young Finns' *(53)*.

The RZS does indeed reduce observer bias, but it does not completely eliminate it. Both, the Hypertension Prevention Trial and the MRFIT demonstrated a marked reduction in terminal digit preference of the corrected BP readings (compared to the uncorrected measurements), and also a roughly bell-shaped distribution of the 'random-zero' values *(51,52)*. Compared to conventional sphygmomanometry, use of the RZS in adults has also been shown to result in a greater intraobserver variability in BP readings *(54)*. While this may seem counterproductive to some, in fact, it more likely indicates the elimination of the bias caused by observer prejudice with the conventional sphygmomanometer that artificially causes multiple BP readings by a single observer to be very close to each other due to knowledge of the prior reading. Identical findings have been reported in children, albeit in a smaller study, when the RZS was compared head to head with the conventional sphygmomanometer *(27)*. While the 'Study of Cardiovascular Risk in Young Finns' did not simultaneously compare the RZS to any other casual method of BP measurement, the design of this longitudinal study was such that on the first two occasions BPs were measured, in a cohort of randomly selected children between 6 and 18 years, using a conventional sphygmomanometer. For the third survey, which was conducted on a subset of the original cohort, the RZS was used *(55)*. Therefore, while the study does not allow one to comment directly on the comparability of the two methods, the results are quite interesting and are in line with the previously mentioned adult data. First of all, this study also demonstrated that, in spite of adequate training, terminal digit preference was almost universally observed in all personnel obtaining BPs (using the conventional sphygmomanometer) during the initial two surveys, while this was almost completely eliminated using the RZS in the third trial. Second, the investigators made an interesting observation that the age-related curves obtained by the two methods differed significantly, with an apparently nonlinear rise in BP (as measured by the conventional method) with age, probably related to observer bias. A more continuous rise in BP with age, as might be expected on a biological basis, was seen when the RZS data was plotted; this was especially noticeable at low BP values. Based on these findings, the study investigators concluded that BPs in children, especially in the lower ranges, are measured more accurately with the RZS compared to the conventional sphygmomanometer, and that the RZS should be the preferred instrument used for epidemiological surveys of BP in this age group.

Notwithstanding all the advantages of the RZS, especially in clinical epidemiology, several concerns have been raised about the accuracy of this instrument including its impracticality due to the bulky design, expense, extent of training needed for personnel to use it accurately, and high maintenance costs. From a practical standpoint, it also shares with the conventional sphygmomanometer the disadvantage of having mercury as an intrinsic component of its design. Many studies have also shown that the RZS, when compared to the conventional sphygmomanometer, systematically underestimates diastolic and systolic BPs, both in adults and in children *(51,55)*. The degree of underestimation varies quite considerably from one study to another, with several studies demonstrating a small and consistent difference of 1–3 mmHg between the two methods *(56,57)*, while others finding a much larger and significant difference *(58)*. This has resulted in contentious debate among investigators; some find the instrument acceptable for use according to the guidelines of the British Hypertensive Society *(56)*, while others strongly advise against its use without further study *(58)*. Whether the 'underestimation' of BP by the RZS is real, or rather is

due more to an 'overestimation' of BP by the conventional sphygmomanometer, is unclear. Numerous reports have emphasized that these differences can be minimized or even eliminated by rigorous attention to the details of the measurement technique, intensive training of personnel *(59)*, and meticulous maintenance of the equipment, which is prone to subtle malfunction *(57,60)*.

In conclusion, although the 'blinded' nature of BP readings using the RZS makes it an ideal candidate instrument for epidemiological studies, the limited data in children and the aforementioned contradictory findings of its accuracy among different investigators, along with the practical issues related to expense, maintenance costs, and need for intensive personnel training, make the use of the RZS very impractical, certainly for routine clinical care, and perhaps also for epidemiological studies pending further research. Ultimately, however, the demise of this instrument will probably be more due to environmental concerns rather than any issues related to its accuracy.

Oscillometric BP Measurement

Oscillometric devices have all but replaced the mercury manometer in a large number of medical centers, especially in European countries where concern about environmental contamination with mercury has been greater *(40)*. Background information on these devices and a discussion related to the advantages and disadvantages of oscillometry are discussed comprehensively in a recent review article *(61)*. In brief, development on the first commercial oscillometric device for BP measurement started in the early 1970s and resulted in the 'Dinamap', an acronym for 'device for indirect noninvasive mean arterial pressure' *(62)*. Since that time, a plethora of oscillometric devices for automated BP measurement have flooded the market, including several new modifications of the original Dinamap model 825 (Critikon division of GE Healthcare, Waukesha, WI). The basic principle underlying these devices is the same as that of other cuff-based BP measuring devices, in that compression of the arm by an inflatable cuff allows indirect determination of the intra-arterial vascular pressure. The difference between conventional sphygmomanometry and the oscillometric devices is that in the latter, cuff inflation and deflation are automated and that BP determination is made by a microprocessor using information sent to it from a pressure transducer; this potentially is tremendously advantageous by eliminating all observer biases. Only a short summary of the process of BP measurement is described herein. More details are available in the articles by Ramsey *(62)*, and Jilek and Fukushima *(63)*. In brief, the BP cuff gets automatically inflated to between 160 and 180 mmHg (or 70 and 125 mmHg in the neonatal mode), depending on the specific device, for the first BP determination and subsequently to 35 mmHg above the previously recorded systolic value. After a brief holding period, the cuff pressure is reduced in a stepwise manner in 5–10 mmHg decrements. As the cuff pressure decreases, oscillations of the arterial wall increase in amplitude and reach a maximum when the cuff pressure approaches the mean arterial pressure. With further deflation of the BP cuff, oscillations of the arterial wall diminish and eventually stop altogether. The monitor uses this information to compute and display values for the mean, systolic, and diastolic BP. The precise method of BP determination is far more complicated and is determined by a complex algorithm that varies from one device to another. It is important to point out here that systolic and diastolic BP readings in oscillometry do not correspond to the point of first appearance and disappearance, respectively, of arterial wall oscillations. The pressures displayed on the monitor, therefore, may be 'calculated' rather than actually 'measured' values, at least for some of the oscillometric devices in the

market. These algorithms have been considered proprietary information and are therefore kept in confidence, making it impossible for investigators to verify the accuracy of their underlying physiological principals. In addition, since the algorithms are proprietary, the devices may not be interchangeable. Some algorithms are based on the ratio of the oscillometric waveform amplitudes, while others are based on the change in slope of the amplitude of oscillations. Supporting this observation is the finding, in one study, that two different oscillometric devices used simultaneously yielded different BP results *(64)*.

Many studies have evaluated the comparability of oscillometric readings with BP readings obtained by invasive means. Park and Menard *(65)* compared the Dinamap model 1846 and a conventional mercury sphygmomanometer with radial artery pressures in a group of infants and children admitted to the intensive care unit. While both the Dinamap model 1846 and the conventional mercury sphygmomanometer readings correlated well with intra-arterial BP measurements, the correlation coefficient was better for BP readings obtained using the Dinamap model 1846. The difference between the Dinamap model 1846 and intra-arterial BP readings was small and ranged from −7 to +7 mmHg, −9 to + 10 mmHg, and −10 to + 8 mmHg for systolic, diastolic, and mean BP, respectively. Similarly, BP readings obtained in infants using the Dinamap model 847 neonatal and Dinamap model 845 vital signs monitor were found to correlate well with BP values obtained using a central aortic catheter, with even smaller mean absolute pressure differences than seen in the previous study *(66),* as shown in Figs. 1 and 2.

However, comparisons between BP readings using a mercury sphygmomanometer and some oscillometric devices, especially the newer models, demonstrate that the two methods are not comparable. A large single-center study evaluating the newer Dinamap model

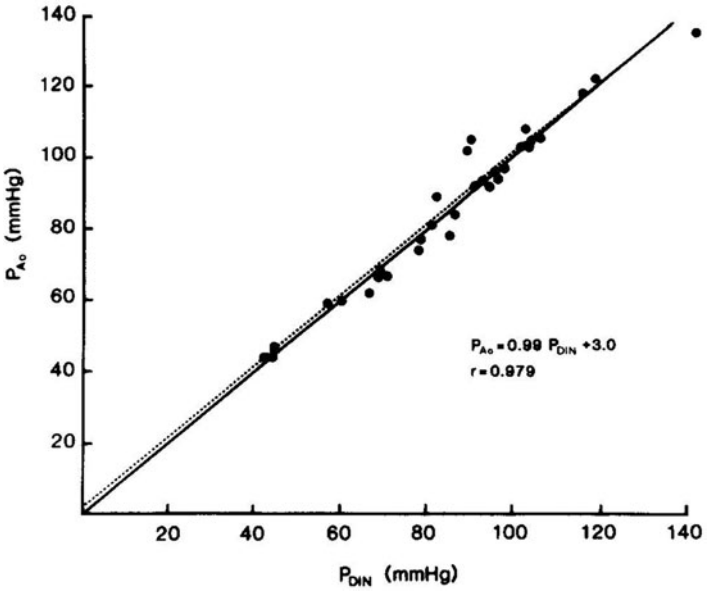

Fig. 1. The relation between central aortic (P_{AO}) and Dinamap (P_{DIN}) measurements for systolic pressure. The linear regression equation and correlation coefficient (*r*) are given. The line of identity (*solid line*) and least-squares regression line (*dotted line*) are shown. (Reproduced with permission from *(66*, figure 2.)

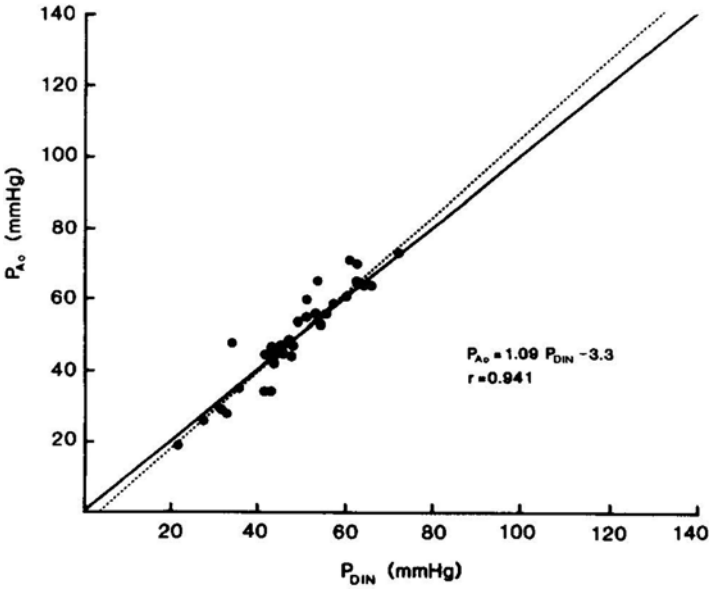

Fig. 2. The relation between central aortic (PAo) and Dinamap (PoIN) measurements for diastolic pressure. The linear regression equation, correlation coefficient, line of identity, and least-squares regression line are given as in Fig. 1. (Reproduced with permission from *(66*, figure 3.)

8100 against the conventional mercury sphygmomanometer in over 7000 children found that the mean Dinamap model 8100 readings were higher for both systolic (by 10 mmHg) and diastolic (by 5 mmHg) values. However, the 95th percentile confidence intervals for differences in systolic and diastolic BPs between the two methods were quite large and ranged from −4 to +24 mmHg and −14 to +23 mmHg, respectively, making the 'error' nonsystematic and unpredictable *(67)*. Similarly, in the Bogalusa Heart Study, significant differences were noted in BPs obtained using the Dinamap model 8100 and a conventional sphygmomanometer. While the mean systolic pressure with the Dinamap model 8100 was higher than that obtained using a conventional sphygmomanometer, similar to the study by Park et al., the mean diastolic pressure was, in fact, lower with the Dinamap model 8100 *(68)*. Moreover, an age-related difference was noted in the discrepancies between the two devices for diastolic BP. In children under 8 years of age, the Dinamap model 8100 diastolic BPs were higher compared to the conventional sphygmomanometer readings, while in children over 8 years, the Dinamap model 8100 underestimated diastolic BP.

To ensure accuracy of oscillometric BP measuring devices two different validation standards are currently in use. These are the British Hypertension Society (BHS) protocol *(69)* and the guidelines put forth by the AAMI *(70)* (Table 2). Since these two protocols can be reconciled, fulfillment of both sets of criteria should be used in validating any oscillometric device. Briefly, the BHS protocol looks at the absolute difference between BPs obtained simultaneously by the oscillometric device and a standard sphygmomanometer in different phases of use (before-use calibration, in-use phase, after-use calibration, and static validation). As the percentage of paired readings that are close to each other increases, the better is the grade assigned to the device (Grades A and B are acceptable while Grades C and D are unacceptable). The AAMI criteria, on the other hand, require that the device being tested be compared either to a standard sphygmomanometer or to direct intra-arterial

Table 2
Protocols for Assessment of the Accuracy of BP Measuring Devices

BHS grading criteria			
Grade	*Difference between test and 'standard' device readings (%)*		
	≤5 mmHg	≤10 mmHg	≤15 mmHg
A	60	85	95
B	50	75	90
C	40	65	85
D	Worse	Worse	Worse
	AAMI criteria		
Grade	*Mean difference between devices (mm Hg)*		*Standard deviation (mm Hg)*
Pass	≤ 5		≤ 8
Fail	≥ 5		≥ 8

readings (especially in neonates, in whom it is often very difficult to hear the Korotkoff sounds). In order to get a passing grade from the AAMI, the test device measurements should not differ from the reference standard by a mean of >5 mmHg and a standard deviation of >8 mmHg. These standards are based upon the assumption, albeit unproven, that the physiological principles that underlie the oscillation of the arterial wall and its relation to BP are somehow identical to the Korotkoff sounds and their relation to BP. While many concerns have been raised about the reproducibility, complexity, and cumbersome nature of these two guidelines, they remain, to date the 'gold standard' for testing new devices in the market *(71)*. As environmental and other pressures increase the prominence of oscillometric devices, it is quite likely that a new set of distinct criteria will be established, much like the standards applied to direct intra-arterial measurements of BP versus auscultatory methods.

Based on the aforementioned guidelines, O'Brien et al. *(72)* recently reviewed several oscillometric devices available in the market and found that only a few fulfilled accuracy criteria for both protocols. Some of the devices that are recommended in this report for use in children are the CAS model 9010 (CAS Medical systems, Branford, CT) for in-hospital use, the Omron HEM-750CP (Omron Health Care, Inc., Vernon Hills, IL) for self-measurement and the Daypress 500 (Neural Instruments, Florence, Italy) for ambulatory BP monitoring, although only at rest. The BHS website (http://www.bhsoc.org/) also lists two other devices that have been validated in children: the Datascope Accutor Plus (Datascope Corporation, Mahwah, NJ) *(73)* and the Omron 705-IT (Omron Health Care, Inc., Vernon Hills, IL) *(74)*. The latter has not been validated in hypertensive children, nor do the data support its accuracy in obese children. Such issues, related to the need for validating devices for children with anthropometric measurements considered outside the realm of 'normal', are significant and worthy of study, considering that we are in the midst of an obesity epidemic. One of the more commonly used oscillometric devices in the United States, the Dinamap model 8100 has yielded varying results when tested for accuracy. Few pediatric studies have followed the strict guidelines of the AAMI and BHS protocols to evaluate the Dinamap model 8100. In a small study in a cohort of prepubertal children (8–13 years old),

compared to the conventional sphygmomanometer, the Dinamap model 8100 was found to overestimate systolic BP and underestimate diastolic BP. These differences, however, were within the range acceptable by both the aforementioned validation standards *(75)*. The mean difference (standard deviation) between the BP readings obtained by the Dinamap model 8100 and the conventional sphygmomanometer was 4.8 (7.5) mmHg for systolic and −1.9 (7.5) mmHg for diastolic BP, making the device acceptable to the AAMI. Similarly, using the BHS criteria, the Dinamap model 8100 achieved a grade of B since more that 50% of its readings were within 5 mmHg and more than 90% were within 15 mmHg of the conventionally obtained measurements. However, other studies have not been as flattering of this device. In a study by O'Brien et al. *(76)* in 1993, the Dinamap model 8100 was evaluated for accuracy in an adult population according to the strict guidelines of the BHS protocol, and found to achieve a grading of D (unacceptable) for diastolic BP and B (acceptable) for systolic BP. Therefore, in the absence of further study in a larger group of children, the use of the Dinamap model 8100 cannot be recommended without reservation.

The 4th Report on high BP in children and adolescents recognized the practical issues related to attempting the auscultatory technique in infants and toddlers and suggested that the use of oscillometric devices in these youngest of children, that is, those less than 3 years of age, was acceptable, especially in settings when repeated measurements were felt to be necessary *(25)*. When oscillometric devices have been studied in neonates, many of the aforementioned issues become critical. One study compared three different oscillometric devices against intra-arterial measurements. Even recognizing that an oscillometric device measures a "different" pressure than a direct arterial line, the authors found significant disagreements between the devices and recommended arterial line measurements in critically ill neonates *(77)*.

Certainly there are discrepancies between auscultatory and oscillometric measurements; these discrepancies are not necessarily 'errors'. Whether the source of the discrepancy is mechanical and in the oscillometric device, or due to observer error with the conventional sphygmomanometer is, at best, speculative. It is also certainly possible that the 'error' arises from a more accurate determination of BP (especially the diastolic BP) by the oscillometric device that may be programmed to calculate values that match more closely to a 'true' intra-arterial BP, thereby eliminating the error inherent in the conventional sphygmomanometer, which necessarily has to rely on the Korotkoff sounds as an indirect and approximate surrogate indicator of true vascular pressure *(78)*. What is clear from studies comparing oscillometric devices with conventional sphygmomanometers is that these two methods of BP measurement should not be used interchangeably and that they may be measuring different biological parameters.

The potential advantage of using oscillometric devices over conventional sphygmomanometry is manifold. First and foremost, they are felt to be convenient, easy to use, and eliminate the need for highly trained personnel, although this may not really be the case *(79)*. Moreover, by avoiding terminal digit preference and bias related to prior knowledge of recorded BPs, the use of these devices, if accurate, can improve measurement precision and substantially lower the sample size required in clinical trials on hypertension. Oscillometric devices are also easier to use in younger children, neonates and infants, in whom movements of the arm may make it difficult to use auscultation to accurately hear the Korotkoff sounds; the success of oscillometric devices in obtaining BPs has been demonstrated in this age group by Park and Menard *(80)*. The use of such devices also eliminates the K4–K5 controversy mentioned previously *(36)*, since the oscillometric devices correlate very well with direct intra-arterial pressures *(65)*. However, the greatest

advantage of these devices may turn out to be an ecological one. Since oscillometric devices do not use mercury, they may eventually supplant all mercury manometers due to the previously mentioned concern about the environmental hazard posed by this element *(40)*. The 4th report attempted to bridge these issues by suggesting that, in health care settings, oscillometric devices can be used, but the readings that exceed the 90th percentile norms be remeasured by an auscultatory method *(25)*.

While oscillometric devices, when correctly chosen, can greatly add to the management of patients with hypertension and improve clinical trials, their use is not without problems. As mentioned before, caution must be advised before a particular device is chosen for use, since the accuracy of many newer devices has not been tested in an unbiased manner. In addition, these are expensive pieces of equipment and also need continued upkeep and servicing to ensure optimal functioning, all of which adds to their cost. Certain drawbacks also exist in the design of these machines. While perhaps not applicable to any great extent in pediatrics, it is noteworthy that the upper limit of systolic pressure that these devices can measure is limited and varies from 240 to 280 mmHg (or about 160 mmHg in the neonatal mode) *(65,81)*.

Difficulties may also arise in BP measurements in children with cardiac arrhythmias and in those who are uncooperative and cannot hold still, leading to motion artifacts *(62)*. Moreover, the rapid rate of inflation of the cuff by the machine to a pressure of 160 mmHg may be uncomfortable and disconcerting to children, and may cause them to resist the BP measurement, leading to erroneously high readings. In fact, a 'first-reading' effect, in which the first of several BP readings is 3–5 mmHg higher than subsequent readings a few minutes later, has been noted by several investigators using oscillometric devices in children *(68,80)*. Therefore, repeat measurements of BP are important in children to avoid the overdiagnosis of hypertension. The optimal number of measurements, per patient and per visit, for oscillometric devices, may vary from machine to machine. For one particular device, the Dinamap model 845 XT, the reliability was noted to increase quite significantly when the number of BP measurements went from three to four per visit, and the number of visits went from one to two *(27)*. Finally, an issue that has irked clinical investigators for long is the knowledge that the algorithms used for determination of BP by oscillometric devices vary from one manufacturing company to another and also between different models of the same device. These algorithms have been considered to be proprietary information, and being confidential, have never been subjected to scientific scrutiny, causing health-care professionals to be somewhat skeptical of their validity *(82)*.

Users of oscillometric devices need to keep in mind a few other issues. As mentioned earlier, BPs obtained by conventional sphygmomanometry and using oscillometric devices should not be used interchangeably for study purposes, since even with the most accurate of devices, differences do exist between the two. Also, since normative data in use at present in children are based on BP measurements obtained by conventional sphygmomanometry *(25)* using these norms to determine if the BP, measured in a particular child using an oscillometric device, is normal, may not be appropriate. Having stated that, it must be noted that some normative reference data on BPs using an oscillometric device are available for children younger than 5 years of age *(80)*. It is also interesting to note that in spite of the aforementioned concerns with the use of oscillometric devices, some epidemiological studies of BP in adults and even one in children (the CATCH trial) are using such devices for BP determination *(83,84)*. Furthermore, it has recently been documented that the Dinamap has been programmed in such a way that it specifically cannot report certain values of BP *(85)*. Finally, we must all remember that, although oscillometric devices eliminate observer

bias, they share with the mercury sphygmomanometer the likelihood that BP readings may be affected by environmental (e.g., ambient temperature) and patient factors (e.g., stress and arm size–cuff size discrepancy).

PROBLEMS WITH CASUAL BP MEASUREMENTS

Having reviewed the various individual methods of casual BP determination in children, we do need to recognize that these methods are not infallible and that there are many concerns related to the use of BPs obtained by such methods. Potential problems have already been discussed separately for each individual method in earlier sections of this chapter, and the reader is referred to these sections for more specific details. Suffice it so say that with meticulous attention to detail and by choosing the instrument appropriate to one's purpose, many of these problems and errors can be avoided. Table 3 compares the pros and cons of the various techniques for measuring BP in children (Table 3).

The second concern with casual BP readings is perhaps a more important and fundamental one. Although cross-sectional normative data on BP in children are routinely used in clinical management, there are no direct studies evaluating the validity of these norms in predicting the risk of adverse events in adulthood. Longitudinal epidemiological studies of BP starting in children, having commenced in the United States in the early 1970s have not had sufficient time to extend their follow-up into late adulthood to establish, if like adults, childhood hypertension or even high BP is predictive of cardiovascular and cerebrovascular morbidity and mortality. More importantly, it is not been shown for certain that early intervention is of any measurable benefit in reducing morbidity and mortality later in life. Indirectly, though, it seems biologically plausible and likely that hypertension starts in childhood and, if persistent, may be a predictor of adult onset morbidity. It would seem equally plausible that BP control in hypertensive children will reduce later morbidity. Resolution of left ventricular hypertrophy in children is seen when hypertension is treated.

The most direct evidence of a possible impact of high BP (either in of itself or by virtue of it being a surrogate marker for children with dyslipidemia, overweight, or insulin resistance) comes from the autopsy studies of the Bogalusa trial and the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) trial, and also from cardiac imaging in participants in the Muscatine study. A subset of children who had participated in the Muscatine trial underwent electron beam computed tomography *(86)* to look for coronary artery calcification (CAC), which has previously been established to correlate well with the presence of atherosclerotic plaques in postmortem specimens *(87)*. An odds ratio of 3.0 (95% confidence interval 1.3–6.7) for CAC at the age of 33 years was noted for adults who were at the highest decile of body mass index in childhood. Although having high BP as a child (8–18 years) was not significantly associated with CAC, the diastolic BP as a young adult (20–34 years) certainly was, with an odds ratio of 4.2 (95% confidence interval 1.9–9.6). The same group of investigators, in a subsequent study, noted an association between CAC and carotid intimal–medial thickness, another marker of atherosclerosis, further cementing the link between BP (in young adults) and risk of future cardiovascular disease *(88)*. The Collaborative Pathology Study, a program of the Bogalusa Heart Study reported autopsy data in 93 children and young adults (2–39 years of age) who had died of traumatic causes *(89)*. These investigators found that the extent of raised fibrous plaques in the coronary arteries, which are known to be precursors of progressive atherosclerosis, correlated positively with antemortem diastolic and systolic BPs. Moreover, the greater the number of cardiovascular risk factors that were present (high body mass index, hypertension, dyslipidemia), the greater was the extent of early atherosclerosis. Finally, the PDAY study

Table 3
Comparison of the Various Methodologies for Casual BP Measurement

	Advantages	*Problems*
Conventional sphygmomanometry (CS)	Easy to use Inexpensive Commonly available Pediatric BP normative data based on it Perhaps the "gold" standard	Operation: observer biases Output: affected by technique, environmental, and mechanical factors (e.g., cuff size) Debate over use of K4 vs K5 as being representative of diastolic BP
Mercury	Minimal maintenance required to maintain calibration Portable; inexpensive Accurate	Environmental issues rehandling, spills, disposal Often not maintained Easily loses calibration
Aneroid	Measures same parameters as mercury	Gauge more subject to bias/misread than Hg column? Often not calibrated
RZS	Reduces observer biases	Design: bulky and difficult to use. Expensive. Uses mercury Operation: extensive training required for correct use Output: BP readings lower than with CS
Oscillometry	Easy to use No mercury in the instrument Frees user to allow more than one thing to be done at the same time Eliminates observer biases Easier to use in infants & young children compared to CS	Design: expensive and requires periodic maintenance Many devices in the market, few of which have been validated for use in children Output: affected by technique, environmental, and mechanical factors (e.g., cuff size) First reading effect High initial inflation pressure may cause anxiety and motion artifacts Limited normative data available for children BP reading not equivalent to CS readings

showed that hypertension augments atherosclerosis in young men and women (15–34 years of age) by accelerating the conversion of fatty streaks in the coronary arteries to raised plaques beginning in the third decade of life and that the effect of hypertension increases with age *(90)*.

So while logic and a significant body of literature would support the contention that hypertension in children, as determined by casual methods, is bad and is worthy of intervention to prevent adverse events in the future, no direct evidence to support this exists in the medical literature thus far. A second consideration, while interpreting casual BP readings obtained by any method, is the appropriateness of using such isolated and intermittent observations for making therapeutic decisions, especially those that might significantly impact on the perceived quality of life of an individual. This brings us back to the question of validity. How valid are casual, as compared to ambulatory, BP readings, in predicting adverse long-term outcomes? While this issue is discussed in greater depth in a subsequent chapter (see Chapter 10), it is important to point out here that discrepancies clearly exist in BP determinations made in an office setting to those obtained at home. A significant body of literature in adults *(91)* and some in children *(92),* points out that a great majority of children with elevated casual BP readings, who would otherwise be classified as being hypertensive by current norms, may actually have 'white-coat' hypertension when ambulatory BP readings are used; this sub-group of children, might perhaps, be at lower or no risk of adverse outcomes, and therefore not merit extensive, expensive and invasive work-up, nor might they require long-term therapy. Preliminary studies have also shown, that like adults, hypertension in children, when determined by ambulatory methods, has a better correlation with risk factors for cardiovascular adverse outcomes such as left ventricular hypertrophy *(93)*. Home BP monitoring is an alternative to ambulatory BP monitoring that has become more prevalent in its use, even in children *(94)*. A further technological advancement in the arena of home BP monitoring relates to the development of telemonitoring systems allowing rapid and easy recording and transmission of home BP data to the health care provider's office. Readers are referred to recently published guidelines from the European Society of Hypertension, which address several issues pertaining to home BP monitoring in great detail, since these are beyond the scope of this chapter *(95)*. Suffice it to say that most studies to date suggest that home BP monitoring is at least as good, if not better than, office BP measurements in predicting adverse outcomes; coupled with its easier availability, lower cost, and convenience compared to ambulatory monitoring, home BP measurements are likely here to stay, but need to be studied in greater depth.

A final note, on the use of wrist BP devices for BP monitoring. None have been validated for use in children. Even in adults, these devices, although commercially available, are subject to errors, especially pertaining to the position of the arm in relation to the heart and are therefore not recommended. Nevertheless, the BHS website does list several such devices that, when used properly, can be used for clinical purposes in adults.

CONCLUSIONS

The concept that there is a "true" BP is probably more obfuscating that illuminating. At any given moment, each of us has a BP, but the force of that pressure will register differently as different systems are used to measure it. Moments later, the pressure is different. Korotkoff himself reported that the first sound heard (K1) appeared before the radial pulse could be palpated as the occluding cuff is deflated *(96)*. K1, on the other hand, is heard after systolic pressure is detected by an indwelling line *(97)*. Mercury and aneroid devices, as discussed earlier, when calibrated properly, agree quite closely on the pressure that they detect. Conversely, oscillometry seems to differ by device and certainly differs from the auscultatory methods, but perhaps comes closest to intra-arterial determinations.

All of these methods, if consistently applied, will correlate with the other, but they are rarely likely to be identical.

The use of casual BP measurements, when performed carefully by trained personnel using calibrated and well-maintained devices, remains the primary screening tool to assess populations for hypertension. The largest pool of normative data in children exists for values obtained by auscultatory methods (albeit the data pooled first BP readings). Auscultatory methods are accurate, but subject to many confounding issues. Oscillometric measures will likely replace auscultatory measures as the primary method of BP determination, but they do not measure the same thing that is auscultated, and they have their own unique set of confounding variables. Additional normal values based upon oscillometry are needed.

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8 Development of Blood Pressure Norms in Children

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Contents

INTRODUCTION

Assessment of blood pressure in children and adolescents, as a measure of health status, is now part of routine clinical practice. Prior to the 1970s blood pressure was not commonly measured in very young children, due to the difficulty in obtaining reliable measurements and the general belief that hypertension was a rare problem in 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 enables clinicians to evaluate the level of blood pressure in a given child relative to age, sex, body size, and other

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_8
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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 healthy, 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 hypertension can be detected in the young, and the value of recognizing the early phase of hypertension is the potential ability to modify the cardiovascular outcome.

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. The outcome of this process is the blood pressure normative data on which we base our current definitions of normotension and hypertension in children and adolescents. This chapter will review that process, and to a large extent, is an 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. Little had been known about the health consequences of hypertension in childhood. Still and Cottom *(2)* provided one of the first descriptions on the outcome of severe hypertension in children by reviewing cases with sustained diastolic blood pressure greater than 120 mmHg that were treated at the Hospital for Sick Children, Great Ormond Street, UK, 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 a 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 time period were limited to children with quite 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 20th 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 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 by a set level of blood pressure, which was similar to values used for adults *(4–6,8)*. The report by Londe *(7)* was based on an examination of younger children, age 4–15 years, and used a different definition of hypertension. Londe had measured blood pressure in his own clinic and observed that blood pressure rises with age, concurrent with growth and development *(6,7)*. He then analyzed the blood pressure data to determine the range of systolic and diastolic

Table 1
Reported Prevalence of Hypertension in Persons 25 Years of Age or Less Prior to Normative Data

Authors	*Subjects age (years)*	*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 BP >90th percentile	12.4 Males 11.6 Females
				Systolic or diastolic BP >95th percentile (repeated measures)	1.9
Wilber et al. *(8)*	15–25	799	Sitting	Systolic>160 Diastolic>90	1.0 1.5

Adapted From Loggie *(3)*.

blood pressure stratified by age, and selected the 90th percentile for each age that defined hypertension. Thus, his reported rates of hypertension are consistent with his definition and are slightly above 10%. He also noted that on repeated measurement, there is 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 the number of children (1.9%) with systolic or diastolic blood pressure equal to or greater than the 95 percentile on repeated measurement is very close to more contemporary data that encompasses 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. The approach to defining abnormal blood pressure in adulthood uses, as the definition of hypertension, the approximate level of blood pressure that marks an increase in mortality that is above average. The cut-point numbers for blood pressure were largely derived from actuarial data from life insurance mortality investigations that indicated an increase in death rates 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 stated to be in "average good health and able to work." Using a statistical method to define the normal range of blood pressure, they described the normal range of systolic blood pressure in males to be 105–135 mmHg at 16 years of age, and rising progressively with age to reach 115–170 mmHg at age 60–64 years. They also noted a gender difference in the normal range with females having a normal range of systolic blood pressure of 100–130 mmHg at 16 years of age, and rising to a normal range of 115–175 mmHg at age 60–64 years. 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 a lower level of systolic blood pressure. Data derived from the Framingham Study in adults have shown that blood pressures in the 130/85 to 139/89 mmHg range have 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 has been developed to designate a range of blood pressure in adults that could benefit from preventive lifestyle changes *(14)*. There are no comparable data that link a level of blood pressure in childhood with 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 age 16–19 years than that in 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 is the prevalence of hypertension in children and adolescents. 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 normal 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 difficulty 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 on cases 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 healthy adolescents. These investigators conducted blood pressure screening on urban high school students. They observed that female students of all races had lower systolic pressures 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 of 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 further examined their data 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 their own data, these investigators suggested that the criteria used to define blood pressure elevations in adolescents would be more meaningful if they were based on the frequency distributions of blood pressure in an adolescent sample and 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 in healthy adolescents were conducted by other investigators, largely in the context of high school screening projects *(21–24)*. The results of these studies also detected initial rates of hypertension, when adult criteria were used, at approximately 5%, and this rate decreased with repeat blood pressure measurements. 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 data derived from a large sample of healthy children.

The gaps in understanding blood pressure and hypertension in childhood were 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. 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 studies conducted in Muscatine, Iowa; Rochester, Minnesota; and Miami, Florida. The total size of the sample was 9,283 children from age 5 through 18 years, with an additional 306 children age 2–5 years (Miami). The blood pressure data were presented as percentile curves, by age, for systolic and diastolic blood pressure in males and females, similar to the standard pediatric growth curves for weight and height.

These blood pressure curves were clearly an advancement, particularly for clinicians who care for children. Although based on cross-sectional data, the curves indicate a normal increase in blood pressure level with age, which 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 95th percentile for each age and sex was the recommended blood pressure level for ascertainment of hypertension, 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. At age 18 years 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, 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 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 in childhood as an indicator of health status. It provided a clear 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 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 in the young within the context of childhood growth, and subsequently supported several epidemiological studies that prospectively investigated blood pressure and growth in children and adolescents. These projects were conducted at several sites, applied rigorous detail to the methodology of blood pressure measurement, and examined the anthropometric determinants of blood pressure 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 2 provides the sites that contributed data that were used to develop the new blood pressure distribution curves. The total number of children on whom blood pressure data was available was over 60,000. This sample included an age range from infancy to 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 in males continued to increase from age 13 through 18 years, whereas the blood pressure in females tended to plateau after age 13 years; and the normal distribution was some-

Table 2
Data Sources for the Second Task Force Report

Source	*Age (years)*	*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

what 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 95th–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 the Sixth Report of the Joint National Commission in 1998 *(10)* that hypertension stage was introduced as a method to guide in patient care and clinical management decisions in adults.

Subsequent to the 1987 Task Force Report, additional childhood blood pressure data were developed from the National Health and Nutrition Examination Survey III *(41)*. There was also reported evidence 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 occurred in the young, rationale was developing for emphasis on blood pressure surveillance in the young, 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. 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 levels at the 90th and 95th percentile for each height percentile and each age from 1 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 were 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 and 139 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 for 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 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 blood pressure measurements on those with an elevated initial blood pressure measurement, the prevalence of hypertension was 3.2% and the prevalence of prehypertension was 15.7% in adolescents *(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 of hypertension and prehypertension combined was over 30% in obese boys and from 23 to 30% in obese girls depending on ethnicity.

A childhood obesity epidemic has been clearly established *(47)*. The association of overweight and obesity with higher blood pressure has been consistently demonstrated in children *(45,46,48)* as well as adults. Rosner et al. *(49)* reexamined the childhood blood pressure normative data based on normal weight children only, and found that the blood pressure percentile curves were only slightly lower, indicating that the sex-, age-, and height-adjusted percentile levels published in the Fourth Working Group report were not confounded by recent increases in the prevalence of childhood obesity. Therefore, the current criteria for high blood pressure in childhood provide important information on population trends in the prevalence of childhood hypertension. An analysis of the trends in childhood blood pressure from two sequential national cross-sectional studies identified a significant increase in both systolic and diastolic blood pressure. The blood pressure increase is most striking among minority groups that also have the highest rates of childhood obesity *(50)*. 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 *(51)*. Both analyses verified that the population increase in blood pressure among children and adolescents is largely due to the increase in prevalence and severity of childhood obesity.

The current blood pressure norms are based on data that have been collected from over 70,000 children and adolescents using rigorous and quite uniform methodology. The population sample from which the data were obtained represents diverse race and ethnic groups from several areas of the USA. 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 development of the childhood normative blood pressure data has been a process that has been underway for many years. The process has benefited by the additions of new information from other areas in the field of hypertension. The process itself has been informative. The current state of knowledge on blood pressure level and blood pressure criteria for hypertension in the young is the outcome of persistent inquiry by many thoughtful clinicians, of the clinical investigators who demanded accurate data on which to base definition, and of the skills of epidemiologists and biostatisticians who developed and analyzed the data. Consideration of the substantial progress which has occurred should provide encouragement to continue forward with the process.

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9 Definitions of Hypertension in Children

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Contents

INTRODUCTION

While noninvasive blood pressure (BP) measurement has been possible for over 100 years *(1)* and has become a routine part of clinical care for all children and adolescents, proper utilization of the information obtained by BP measurement remains an evolving process. This chapter will review a brief history of the recognition of hypertension (HTN) in children, currently accepted definitions of HTN for children and adolescents, strengths and limitations associated with these definitions, and considerations for further improving these definitions in the future.

HISTORICAL ASPECTS

As late as the 1940s, elevated BP was considered a natural response to improve circulation to major organ systems such as the heart, brain, and kidneys, and interfering with this so-called essential hypertension was believed to potentially cause more harm than

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_9
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good. President Franklin Delano Roosevelt who developed HTN in 1937 at the age of 55 was a typical example of those with untreated HTN during this era. He went on to develop left ventricular hypertrophy, congestive heart failure, multiple lacunar infarcts, and chronic kidney failure, ultimately dying from a cerebral hemorrhage just 8 years later *(2,3)*. While dramatic changes in the diagnosis and treatment of HTN in adults would occur over the next several decades, it was not for at least another quarter of a century that it was recognized that children might also have high BP.

One of the first investigators to be interested in childhood BP was Sol Londe, who measured BP in healthy children and noted an increase in BP relative to age, growth, and development *(4)*. He performed further analyses of the limited BP data available and described ranges of systolic and diastolic BP stratified by age as well as how children's BP tends to regress to the mean with repeated measurement. However, what was lacking at that time was a clear definition of what constituted elevated BP in children, which led to uncertainty over establishing the true prevalence of high BP in the pediatric population.

Recognizing the increased interest regarding BP in the pediatric age group, in 1977 the National Heart, Lung, and Blood Institute convened the First Task Force on Blood Pressure Control in Children *(5)* to provide specific guidelines to physicians and other healthcare providers involved in school- and community-based healthcare programs. Lacking good evidence, most of the recommendations for the diagnosis, evaluation, and management of children with elevated BP in this document were opinion based. However, this report did contain the first charts describing normal BP percentiles for children aged 2–18 years. Compiled from data collected at three centers on over 11,000 children, these charts would become the foundation for our current understanding of normal BP patterns in children. As new evidence and normative BP data have become available, these recommendations have been updated on three subsequent occasions, with the most recent report published in 2004 *(6)*. These consensus recommendations constitute the prevailing accepted criteria for diagnosing HTN in children not only in the United States but also throughout the world.

HYPERTENSION AS DEFINED BY CASUAL BLOOD PRESSURE MEASUREMENTS

Traditionally, the mainstay of the diagnosis of HTN has been based on office (or casual) BP measurements. While auscultatory methods using a mercury manometer are still considered the gold standard for BP measurement, advances in technology and environmental concerns regarding mercury toxicity have led to this procedure largely being replaced by automatic oscillometric techniques or auscultatory measurements using an aneroid sphygmomanometer. Although it is beyond the scope of this chapter to discuss the differences in these measurement techniques, it is important to keep these differences in mind when discussing definitions for childhood HTN, as the bulk of the normative BP data used to define BP in childhood were from studies that utilized mercury manometers.

Significant resources have been invested in understanding the short- and long-term effects of elevated BP, the thresholds at which significant morbidity and mortality related to high BP occur, and the benefits of therapy at various stages of this disease process in adults. This research forms the basis for the definitions used to diagnose HTN in adults and has most recently been summarized in the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) *(7)*. Research attempting to define truly abnormal BP in children, however, is somewhat limited given the time that typically lapses between the development of elevated BP

at a young age and morbid events such as myocardial infarction or stroke and the expense involved in conducting such a prolonged study.

Given the lack of such "hard" cardiovascular end points in children, a statistical approach *(8)* based upon the distribution of BP in childhood was adopted by Londe to define high BP in childhood. This approach was also incorporated into the first definitions of childhood HTN by the NHLBI Task Force *(5)* and has continued to be followed in all subsequent Task Force and Working Group reports. While the current consensus recommendations from the NHLBI Working Group *(6)* continue to be based on expert opinion, the normative data on childhood BP are now derived from over 83,000 measurements and therefore provide a much more stable definition of childhood HTN than had been possible in the past *(9)* (Tables 1 and 2). In the future, it may be possible to utilize the mounting evidence that elevated childhood BP is associated with early surrogate markers of target organ damage such as left ventricular hypertrophy and increased carotid artery intima–media thickness to develop evidence-based definitions of HTN in children and adolescents *(10,11)*.

Currently, children with a BP ≥95th percentile for age, gender, and height on three separate occasions should be classified as hypertensive and evaluation and management initiated as recommended (see Table 3). These measurements should be made using auscultatory methods (ideally with a mercury manometer) and Korotkoff sounds 1 and 5 used to define systolic and diastolic BP, respectively. Previous recommendations did suggest that the fourth Korotkoff sound be utilized for diastolic BP, as in some young children Kortokoff sounds can be heard down to 0 mmHg. However, to be consistent with adult recommendations, this is no longer recommended and instead an attempt should be made to repeat the BP reading using less pressure on the stethoscope. If the fifth Korotkoff sound still cannot be determined, the fourth sound should be recorded as diastolic BP for these individuals, with appropriate notation.

Elevation of either systolic or diastolic BP (or both) denotes the child as having high BP. It is also now recommended that HTN in children be staged to indicate the severity of BP elevation (Table 3). Children with a BP ≥95th percentile through the 99th percentile plus 5 mmHg should be classified as having Stage 1 HTN, while those with a BP ≥99th percentile plus 5 mmHg should be considered to have Stage 2 HTN and receive more immediate evaluation and management. It should be noted that the addition of 5 mmHg to the 99th percentile for staging was an arbitrary decision made by the most recent Working Group, who felt this would be appropriate due to the small difference (typically 7–9 mmHg) between the 95th and 99th percentiles *(6)*.

In addition, children and adolescents with a BP ≥90th percentile (or 120/80 when the 90th percentile exceeds this value) but <95th percentile should be considered prehypertensive. This is a new designation as of 2004 for the care of children with elevated BP and was not meant to be considered a diagnosis such as with HTN. Rather the goal of classifying children as prehypertensive is to identify those who may be at risk for development of HTN in the future in the hopes that lifestyle interventions might be instituted in order to prevent its development. Consequently, classifying a child as prehypertensive does not require three repeated measures across time as is required for a diagnosis of HTN.

There are a number of limitations to diagnosing HTN in this manner. First, it should be remembered that diagnosing HTN is dependent on the measurement techniques used to obtain these BP readings. Personnel must pay close attention to procedures used to measure BP to prevent misdiagnosing children with HTN based on erroneous measurements that could be obtained by using the wrong size BP cuff, improper patient positioning, and other common errors in BP measurement *(6)*. In addition, measuring BP in a clinical setting introduces the potential for a white coat effect (persistently elevated BP in a clinical setting

Table 1
Blood Pressure Levels for Boys by Age and Height Percentile[a]

		Systolic BP (mmHg)							*Diastolic BP (mmHg)*						
Age (years)	*BP Percentile ↓*	*← Percentile of height →*							*← Percentile of height →*						
		5th	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*	*5th*	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89

Table 1
(continued)

Age (years)	*BP Percentile ↓*	*Systolic BP (mmHg)* ← *Percentile of height* →							*Diastolic BP (mmHg)* ← *Percentile of height* →						
		5th	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*	*5th*	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP, blood pressure.

[a]To use the table, first plot the child's height on a standard growth curve (www.cdc.gov/growthcharts). The child's measured SBP and DBP are compared with the numbers provided in the table according to the child's age and height percentile.

Reproduced from *(6)*.

Table 2
Blood Pressure Levels for Girls by Age and Height Percentile[a]

		Systolic BP (mmHg)							*Diastolic BP (mmHg)*						
		← *Percentile of height* →							← *Percentile of height* →						
Age (years)	*BP Percentile* ↓	*5th*	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*	*5th*	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87

Table 2
(continued)

Age (years)	BP Percentile ↓	*Systolic BP (mmHg)* ← *Percentile of height* →							*Diastolic BP (mmHg)* ← *Percentile of height* →						
		5th	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*	*5th*	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

BP, blood pressure.

[a]To use the table, first plot the child's height on a standard growth curve (www.cdc.gov/growthcharts). The child's measured SBP and DBP are compared with the numbers provided in the table according to the child's age and height percentile.

Reproduced from *(6)*.

Table 3
Classification of Casual BP in Children and Adults

HTN classification	*2004 Working Group (percentile)*	*JNC VII (mmHg)*
Normotensive	<90th	<120/80
Prehypertensive	90th to <95th or if BP ≥120/80 mmHg even if <90th	120–139/80–89
Stage 1 HTN	95th–99th + 5 mmHg (at three separate visits)	140–159/90–99
Stage 2 HTN	>99th + 5 mmHg (at three separate visits)	≥160/100

HTN, Hypertension

with normal BP in other environments) and may miss children with elevated BP at other times of the day such as in the case of those with isolated nocturnal HTN which may occur with sleep apnea or other chronic medical conditions. It should also be noted that BP is a dynamic process that is constantly changing and that any one BP represents only a small snapshot of the larger process. Thus, many practitioners routinely obtain multiple readings not only across time as recommended by the Working Group but also at any one given office visit. BP readings tend to fall with this approach as a result of both an accommodation effect and a regression to the mean.

This natural variation in BP creates another challenge in defining HTN according to the Working Group guidelines. Classifying hypertensive individuals as Stage 1 or Stage 2 may be difficult as BP can shift across these categories between measurement sessions. In fact, a recent study by McNiece et al. *(12)* showed that only 56% of hypertensive students in a school-based screening had a BP that was classified in the same category on all three required visits. There are no current recommendations from the Working Group on how to address this variability when classifying patients. However, in this study, there was little difference in the ultimate classification of students with Stage 1 versus Stage 2 HTN when staged according to three different possible criteria: (1) BP stage most frequently observed across the three measurement sessions, (2) mean of all BP readings across the three measurement sessions, and (3) stage of BP at final screening.

The same variability is also present when considering BP in the prehypertensive range. Acosta et al. showed that among students in a school screening setting with a mean BP ≥90th percentile (or 120/80) on three separate visits not meeting criteria for confirmed HTN, only 35% were prehypertensives at all three visits *(13)*. The rest fell in the hypertensive range at least once. Another 151 students (out of 1,010 participating) had an elevated BP that subsequently normalized. Understanding what the variability of BP in this range means may ultimately be even more important than understanding BP variability in the hypertensive range as the risk associated with different variability patterns for the development of HTN does not appear to be equal *(14)*. In addition, there may be a subgroup of those with prehypertension who already exhibit target organ abnormalities and thus may not be appropriately classified *(15)*.

Finally, it must be remembered that the normative BP values utilized by the Working Group in forming their recommendations were generated from a population of children and adolescents from the United States and may not be representative of other populations around the world. There have been a number of additional series of "normal values" published in other populations. Some including pooled data from across Europe of 28,043 children *(16)* and another series of 11,519 Italian children *(17)* utilized auscultatory methods, while more recent surveys collected in northern Europe *(18)* and Hong

Kong Chinese children *(19)* have attempted to generate oscillometric norms. None of these series however contain sample sizes comparable to the large database utilized to generate the Working Group charts, and so they currently remain the primary reference used throughout the world, recognizing that there may be potential limitations when applied to non-American children.

HYPERTENSION AS DEFINED BY AMBULATORY BLOOD PRESSURE MEASUREMENTS

Ambulatory BP monitoring provides a technique for assessing BP that addresses many of the limitations of casual BP measurements noted above. Typically worn for 24 hours, these monitors are programmed to measure BP at regular intervals (every 15–30 min) while an individual continues to perform all of his/her normal activities. Thus, this monitoring technique gathers enough data to portray the "bigger picture" of an individual's BP allowing for a better description of BP variability within that individual's natural environment. A number of auscultatory and oscillometric ambulatory devices are available, although only a few have been independently validated in a pediatric population *(20–23)*.

Normal values for ambulatory monitoring have been generated from healthy populations of children as was done for casual measurements. The most commonly referenced are those generated from a population of 1,141 German children in 1997 *(24)*. Several years later, these data were reanalyzed to account for the non-normality of some of the BP curves likely related to the small sample size of the study *(25)*. These "LMS transformed" BP normal values are likely superior to the original normal values published by this group and have been recommended as the best currently available data for interpreting ambulatory BP monitoring studies *(26)*. Several different outcomes, including mean BP for the entire 24 h or for separate awake and sleep periods, can ultimately be assessed using ambulatory monitoring. And as with casual measurements, a mean BP $\geq$95th percentile is typically considered abnormal except among special at-risk populations when the 90th percentile is considered more appropriate. In addition, several other outcomes such as BP load (percentage of time BP is elevated) and percent fall in BP at night may be used by some to diagnose HTN via ambulatory monitoring. A recent consensus report on pediatric ambulatory BP monitoring from the American Heart Association has proposed standard definitions for normal and abnormal ambulatory BP *(26)* which incorporates several of these different parameters.

As with casual measurements, there are limitations in utilizing ambulatory BP monitoring to diagnose HTN. Chief among these limitations is that the most widely utilized normal ambulatory BP values were generated from a racial/ethnically nondiverse population, and may therefore not be applicable to more diverse populations. Also, substantially fewer children were included in this analysis compared to that for the normal values for casual measurements. Ambulatory normal values were generated using an oscillometric device. There is little difference noted in diastolic BP with increasing height in these BP curves as is seen for systolic BP. Whether this is related to a limitation in the monitor's ability to measure diastolic BP or an insufficient sample size to accurately define these differences is not known. In addition, whether these normal values can be applied to measurements obtained using auscultatory monitors or other oscillometric monitors, given the proprietary differences between manufacturers *(27)* for calculations used to determine systolic and diastolic BP from the mean arterial BP measured by the oscillometric monitor, is also unknown.

Although use of ambulatory monitoring in children as young as 2 years has been reported, it is typically not useful in children under 5 years of age because of their ability to comply with the procedure. Equipment is also expensive and several key parameters for interpreting ambulatory BP monitoring such as the minimal time and number of readings required for a monitoring report to be considered complete have not been standardized by experts in the field although the recent recommendations published by the American Heart Association *(26)* should help with this. For these reasons, ambulatory BP monitoring is still only recommended for routine use by experts in the field of pediatric hypertension.

Despite these limitations, ambulatory BP monitoring correlates to early target organ damage such as left ventricular hypertrophy *(28–30)* more closely than casual measurements just as it predicts long-term cardiovascular outcomes in adults *(31–34)*.

COMBINING CASUAL AND AMBULATORY BLOOD PRESSURE MEASUREMENTS

Considering both casual and ambulatory BP measurements together provides a more powerful means of diagnosing HTN. With this approach, four different diagnoses become possible (Table 4). True HTN and true normotension are conditions in which casual and ambulatory measurements agree. Alternatively, white coat HTN is a condition in which casual measurements are consistently elevated while ambulatory measurements are normal, and masked HTN is the inverse condition in which casual measurements are normal but ambulatory measurements are elevated. Recent recommendations for the clinical diagnosis of these conditions are summarized in Table 5.

White Coat Hypertension

White coat HTN is a commonly recognized condition and has a reported prevalence of 1.2–62% of children and adolescents *(35–38)*. This large variation is likely due to differences used to define abnormal BP by both casual and ambulatory means. Its true prevalence is likely closer to 20% as is seen in adult populations *(39)*. While white coat HTN was originally thought to be a benign condition, emerging evidence suggests that it may be at the least a prehypertensive state.

In adults, Verdecchia et al. *(40)* showed that the risk for stroke among adults with confirmed HTN is twice that for those with white coat HTN and normotension at 6 years. However, after 9 years, the risk for stroke among those with baseline white coat HTN exceeded those with ambulatory HTN, suggesting that many of these individuals will go

Table 4
Combining Casual and Ambulatory BP Measurements

		Casual BP measurements	
		Normal	*Elevated*
Ambulatory BP measurements	Normal	Normotension	White coat HTN
	Elevated	Masked HTN	HTN

BP, Blood pressure

Table 5
Suggested Schema for Staging of Ambulatory BP Levels in Children

Classification	*Clinic BP[a] (percentile)*	*Mean ambulatory SBP[b] (percentile)*	*SBP load (%)*
Normal BP	<95th	<95th	<25
White coat HTN	>95th	<95th	<25
Masked HTN	<95th	>95th	>25
Prehypertension	>95th	<95th	25–50
Ambulatory HTN	>95th	>95th	25–50
Severe ambulatory HTN (at risk for end-organ damage)	>95th	>95th	>50

Adapted from Urbina et al. *(26)*.
[a]Based on the National High Blood Pressure Education Program Task Force Standards.
[b]Based on ABPM values of Soergel et al. or the smoothed values of Wuhl.

on to develop significant hypertensive disease. Although studies in children have not consistently demonstrated a relationship between white coat HTN and target organ damage such as left ventricular hypertrophy and increased carotid artery intima–media thickness, several recent reports have reported a trend in increasing left ventricular mass index among adolescents with white coat HTN when compared to those with normal BP *(29,38,41,42)*. Thus, until further evidence is available, counseling children with white coat HTN and their parents regarding lifestyle changes to prevent the future development of HTN and closely monitoring BP, possibly with repeat ambulatory BP monitoring, is likely prudent *(11)*.

Masked Hypertension

Masked HTN was only recently described but has now been clearly documented in several pediatric populations occurring at a rate of 7.6–11% *(35,38,43)*. Adults with masked HTN have a similar risk for long-term cardiovascular morbidity as those with confirmed HTN *(44)*. In addition, children with masked HTN have a similar left ventricular mass index as their hypertensive counterparts *(29,35,38)*. Diagnosing masked HTN, though, is clearly a challenge as these children have a normal clinic BP and there are no other clearly identified characteristics of this condition to help decide which children should be screened for it. Developing approaches to identify these children, however, will likely be critical in preventing long-term cardiovascular morbidity and mortality.

FUTURE DEFINITIONS OF HYPERTENSION

As discussed above, the most significant weakness of essentially all currently accepted definitions for HTN in children is their dependence on normal values generated from a "healthy" population. In contrast, definitions for HTN in adults are based on multiple long-term studies, showing an increased risk of cardiovascular morbidity and mortality in those with an elevated BP. In children, however, these definite cardiovascular outcomes

(such as myocardial infarction and stroke) do not typically occur until many years after the development of HTN. Thus, recent studies in children have focused on surrogate measures of cardiovascular morbidity such as left ventricular hypertrophy and increased carotid artery intima–media thickness, both of which are now well-established cardiovascular abnormalities seen in hypertensive adolescents. Refining definitions for HTN based on these measurable cardiovascular abnormalities will be crucial if a diagnosis of HTN in childhood is utilized to make interventions designed to reduce long-term cardiovascular morbidity and mortality. Indeed, some authors have recently advocated a more aggressive approach to childhood BP based upon the data on surrogate markers already available *(10)*.

One interesting example of an attempt to generate evidence-based interventions to reduce the sequelae of childhood HTN is the ESCAPE trial, a large multicenter study conducted in Europe on the effects of different levels of BP control on the progression of chronic kidney disease *(45)*. In this study, Wuhl et al. showed that controlling BP in a group of 3–18-year olds with chronic kidney disease to below the 50th percentile by ambulatory monitoring slowed their decline in renal function when compared to those whose BP was maintained between the 50th and 95th percentile. This goal for BP control is clearly much lower than the currently recommended target of the 90th percentile for children with chronic kidney disease *(6)*.

Similar studies are needed for defining prehypertension aimed at determining exactly which children are at risk for the more immediate development of confirmed HTN. Recent evidence suggests that current definitions for prehypertension may not be adequately identifying all those at risk. In a recent study of 1,006 adolescents *(14)*, those with a baseline mean BP that was initially ≥95th percentile but who normalized to <90th percentile on subsequent measurement sessions had a sixfold increased rate for the development of HTN when compared to those with a normal BP at baseline. These are children who are currently considered normotensive by Working Group definitions.

In conclusion, our ability to diagnose HTN and early cardiovascular disease in children has progressed substantially over the last 40 years. However, there are still many unanswered questions that must be addressed in order to achieve evidence-based definitions that will accurately identify all those with an increased risk for cardiovascular events and provide therapeutic goals which will decrease this risk.

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10 Ambulatory Blood Pressure Monitoring Methodology and Norms in Children

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Contents

INTRODUCTION

In recent years ambulatory blood pressure monitoring (ABPM) has become the method of choice for the diagnosis and therapeutic monitoring of arterial hypertension in pediatric as well as in adult patients *(1–5)*. ABPM permits a more representative observation of blood pressure (BP) throughout day and night in a non-medical environment. Moreover, ABPM allows to quantify the circadian and even ultradian BP variability *(6–8)*.

While in adult patients ABPM confers a superior prognostic value for end-organ damage as compared to casual blood pressure measurements *(9–12)*, clinical endpoint assessments are still lacking for childhood-onset hypertension. Therefore, while fixed, risk-adapted cut-off levels for optimal, normal, high normal, and elevated blood pressure (BP) have been defined for the adult population *(13,14)*, pediatric targets are derived from the distribution of BP in the general pediatric population.

Although ABPM is widely used in children, there are still some open issues concerning normative data sets in infants and younger children, optimization of protocols for monitoring BP and data analysis, and appropriate validation of devices for use in the pediatric population.

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_10
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METHODS FOR MEASURING AMBULATORY BLOOD PRESSURE

ABPM Monitors

Recommendations for the use of ABPM are included in all recent guidelines for diagnosis and treatment of high blood pressure in adults as well as in children *(13–16)*. However, some of the recommendations made for adults are not easily transferable to pediatrics.

The equipment tested and approved for adults is often not explicitly validated for use in children. The ideal device should be validated for measurements in children, lightweight, equipped with small cuff sizes starting from the infant range, and should have a robust hardware and software suitable for use in physically active children without producing too many erroneous measurements *(17)*.

As for casual BP measurements, the cuff width should cover at least 40%, and the cuff length 80–100%, of the upper arm circumference *(16)*. Cuffs are available starting from neonate size; however, validation data for this age range are missing. Standard cuff sizes for the use in infants start at 12 cm upper arm circumference. These will allow ABPM measurements from the age of 6 months onward. Measurements in infants below 2 years of age are feasible, and the number of erroneous measurements seems to be even lower than in the 3- to 5-year olds *(18,19)*, possibly due to greater physical activity and lower acceptance of the measurement procedure in preschool age. However, normative data sets for infancy are still restricted to small sample sizes *(18,19)*.

Regarding measurement technology, both auscultatory and oscillometric ABPM devices are available. The limitations of both methods are comparable to those described for casual BP devices *(16,20)*: Auscultatory ABPM devices are better graded regarding accuracy and durability according to national US (AAMI *(21)*) and British protocols (BHS *(22)*). Nevertheless, measurements are more prone to movement artifacts and the controversy which Korotkoff sound more accurately defines diastole (K4 vs. K5) has not been uniformly solved by the manufacturers. Moreover, comprehensive normative data for auscultatory ABPM devices are lacking. Oscillometric devices usually have less erroneous measurements than auscultatory devices (4 vs. 30% of measurements *(23)*) and are easier to use, although grading according to AAMI or BHS standard protocols is lower. Systole and diastole are not measured directly but are derived mathematically from mean arterial pressure by device-specific algorithms; as a result differences between oscillometric measurements and auscultatory devices used for validation are common *(20)*. However, most normative ABPM values published are oscillometric data *(3,18,19,24–26)*, and oscillometric devices are widely used in pediatric hypertension clinics.

Information on currently available ABPM monitors that have undergone independent testing and passed national standards (AAMI or BHS) is provided by the web site www.dableducational.org or the respective web sites of the national hypertension leagues (e.g., American Society of Hypertension, British Hypertension Society, Deutsche Hochdruckliga). Only devices that passed these tests should be used.

The software equipment of the monitors is variable. As a minimum requirement the frequency of measurements should be programmable and the software should allow entering pediatric 95th percentile cutoffs (*(24,25)*, see Table 1). The mean 24-h, daytime, and nighttime systolic, diastolic, and mean arterial pressure as well as BP load should be reported. Mean BP levels should be compared with normative values. In addition the nocturnal BP dipping, i.e., the percent day–night difference [(mean daytime BP – mean nighttime BP)/mean daytime BP × 100], should be determined for systolic and diastolic BP (Fig. 1).

Table 1
Ambulatory Blood Pressure Values for Healthy Caucasian Children

	a. Normative ABPM values (mmHg) for boys by age (years)											
	Age (years)											
BP percentile	*5.0*	*6.0*	*7.0*	*8.0*	*9.0*	*10.0*	*11.0*	*12.0*	*13.0*	*14.0*	*15.0*	*16.0*
24-h SBP												
50th	104.6	105.5	106.3	107.0	107.7	108.8	110.4	112.6	115.1	117.8	120.6	123.4
75th	109.0	110.0	111.0	111.9	112.8	114.1	115.9	118.2	120.9	123.7	126.5	129.4
90th	113.4	114.7	115.8	116.8	117.9	119.2	121.2	123.7	126.4	129.3	132.1	134.9
95th	116.4	117.7	118.9	120.0	121.1	122.5	124.6	127.1	129.9	132.7	135.5	138.2
99th	122.7	124.1	125.4	126.6	127.7	129.2	131.4	134.0	136.9	139.5	142.0	144.5
Daytime SBP												
50th	111.1	111.5	111.9	112.2	112.6	113.4	114.9	117.0	119.5	122.3	125.3	128.2
75th	115.7	116.3	116.8	117.3	117.9	118.8	120.5	122.9	125.6	128.5	131.5	134.6
90th	120.1	120.9	121.6	122.2	122.9	124.0	125.9	128.4	131.2	134.2	137.3	140.4
95th	122.9	123.8	124.6	125.3	126.1	127.3	129.3	131.8	134.7	137.7	140.8	143.9
99th	128.5	129.6	130.6	131.5	132.3	133.7	135.8	138.6	141.5	144.4	147.4	150.4
Nighttime SBP												
50th	95.0	95.5	96.1	96.7	97.3	98.1	99.4	101.2	103.4	105.8	108.3	110.9
75th	99.2	100.2	101.1	102.0	102.9	103.9	105.3	107.1	109.3	111.9	114.4	116.9
90th	103.4	104.9	106.2	107.5	108.5	109.6	111.0	112.8	115.0	117.5	120.0	122.5
95th	106.3	108.0	109.6	111.0	112.1	113.2	114.6	116.3	118.6	121.0	123.4	125.9
99th	112.3	114.6	116.7	118.4	119.6	120.7	121.9	123.4	125.5	127.8	130.1	132.3
24-h DBP												
50th	65.3	65.7	66.1	66.3	66.5	66.6	66.9	67.2	67.4	67.7	68.1	68.6
75th	68.8	69.3	69.6	69.9	70.0	70.2	70.5	70.8	71.0	71.4	71.8	72.3
90th	72.2	72.6	73.0	73.2	73.3	73.4	73.7	74.0	74.3	74.6	75.1	75.6
95th	74.4	74.8	75.1	75.2	75.3	75.4	75.7	75.9	76.2	76.6	77.0	77.5
99th	78.9	79.0	79.1	79.1	79.1	79.1	79.3	79.6	79.9	80.2	80.7	81.3
Daytime DBP												
50th	72.2	72.4	72.5	72.5	72.3	72.1	72.0	72.0	72.2	72.5	73.0	73.5
75th	75.9	76.1	76.3	76.4	76.2	76.0	76.0	76.0	76.2	76.5	77.0	77.6
90th	79.1	79.3	79.7	79.8	79.7	79.5	79.5	79.5	79.7	80.0	80.6	81.3
95th	81.0	81.3	81.6	81.8	81.7	81.5	81.5	81.6	81.7	82.1	82.8	83.5
99th	84.5	84.8	85.2	85.5	85.4	85.3	85.3	85.4	85.6	86.1	86.8	87.7
Nighttime DBP												
50th	55.0	55.3	55.5	55.7	55.8	55.8	55.9	56.0	56.3	56.5	56.8	57.1
75th	58.5	59.1	59.5	59.8	60.0	60.0	60.0	60.1	60.3	60.5	60.7	60.9
90th	62.3	63.2	63.8	64.2	64.3	64.2	64.1	64.1	64.1	64.2	64.3	64.3
95th	65.1	66.1	66.8	67.1	67.1	66.9	66.7	66.5	66.5	66.5	66.4	66.4
99th	71.6	72.7	73.5	73.5	73.2	72.6	71.9	71.4	71.1	70.8	70.6	70.3
24-h MAP												
50th	77.4	77.9	78.7	79.3	79.7	80.2	80.8	81.7	82.7	83.8	85.1	86.4
75th	81.4	81.9	82.7	83.4	83.8	84.3	85.0	85.9	86.9	88.0	89.3	90.5

Table 1
(continued)

a. Normative ABPM values (mmHg) for boys by age (years)

	Age (years)											
BP percentile	*5.0*	*6.0*	*7.0*	*8.0*	*9.0*	*10.0*	*11.0*	*12.0*	*13.0*	*14.0*	*15.0*	*16.0*
90th	85.5	86.0	86.8	87.4	87.9	88.3	88.9	89.7	90.6	91.6	92.7	93.9
95th	88.3	88.7	89.5	90.0	90.4	90.8	91.3	91.9	92.7	93.7	94.7	95.7
99th	94.3	94.6	95.1	95.4	95.6	95.7	95.8	96.2	96.7	97.3	98.1	98.9
Daytime MAP												
50th	83.5	84.1	84.5	84.8	84.9	85.0	85.3	85.9	86.8	88.0	89.4	90.8
75th	87.5	88.2	88.8	89.2	89.4	89.5	89.9	90.6	91.5	92.7	94.2	95.7
90th	91.3	92.1	92.8	93.3	93.5	93.7	94.0	94.7	95.6	96.8	98.3	99.8
95th	93.6	94.5	95.3	95.8	96.1	96.2	96.5	97.1	98.0	99.2	100.6	102.1
99th	98.2	99.2	100.1	100.7	101.0	101.0	101.2	101.6	102.4	103.4	104.7	106.1
Nighttime MAP												
50th	66.7	67.7	68.6	69.2	69.7	70.0	70.5	71.2	72.1	73.1	74.0	74.9
75th	70.5	71.7	72.8	73.5	74.1	74.5	75.0	75.6	76.4	77.2	78.0	78.6
90th	74.7	76.0	77.2	78.1	78.6	78.9	79.3	79.7	80.3	80.8	81.3	81.7
95th	77.6	79.0	80.2	81.1	81.6	81.8	82.0	82.3	82.6	82.9	83.2	83.4
99th	84.1	85.7	86.9	87.6	87.8	87.7	87.4	87.1	86.9	86.8	86.6	86.4

b. Normative ABPM values (mmHg) for boys by height (cm)

	Height (cm)												
BP percentile	*120.0*	*125.0*	*130.0*	*135.0*	*140.0*	*145.0*	*150.0*	*155.0*	*160.0*	*165.0*	*170.0*	*175.0*	*180.0*	*185.0*
24-h SBP														
50th	104.5	105.3	106.2	107.2	108.3	109.5	110.9	112.5	114.2	116.1	118.0	119.7	121.5	123.2
75th	109.2	110.1	111.1	112.1	113.3	114.6	116.1	117.7	119.5	121.4	123.2	125.0	126.6	128.2
90th	113.8	114.8	115.9	116.9	118.2	119.5	121.0	122.6	124.4	126.3	128.1	129.8	131.3	132.8
95th	116.8	117.8	118.9	120.0	121.2	122.5	124.0	125.7	127.4	129.3	131.1	132.6	134.1	135.5
99th	122.9	123.9	125.0	126.1	127.3	128.6	130.1	131.7	133.4	135.2	136.8	138.2	139.4	140.5
Daytime SBP														
50th	110.8	111.1	111.5	112.0	112.7	113.7	115.1	116.8	118.6	120.6	122.6	124.4	126.2	128.0
75th	116.2	116.5	116.9	117.4	118.0	119.0	120.4	122.1	124.2	126.4	128.4	130.3	132.2	134.1
90th	121.7	121.9	122.2	122.5	123.0	123.9	125.3	127.1	129.4	131.9	134.1	136.1	138.0	139.9
95th	125.2	125.3	125.5	125.7	126.0	126.9	128.3	130.2	132.7	135.3	137.6	139.6	141.6	143.5
99th	132.6	132.4	132.2	132.0	132.1	132.8	134.2	136.3	139.1	142.2	144.7	146.8	148.6	150.5
Nighttime SBP														
50th	93.6	94.6	95.6	96.7	97.9	99.0	100.1	101.3	102.6	104.1	105.6	107.2	108.7	110.2
75th	98.6	99.8	101.0	102.3	103.6	104.7	105.9	107.1	108.4	109.9	111.5	113.1	114.6	116.1
90th	103.3	104.8	106.3	107.8	109.3	110.6	111.8	113.0	114.3	115.7	117.2	118.8	120.3	121.8
95th	106.3	107.9	109.7	111.4	113.0	114.4	115.7	116.8	118.1	119.4	120.9	122.4	123.9	125.3
99th	112.1	114.2	116.5	118.7	120.8	122.5	123.8	124.9	126.0	127.1	128.4	129.6	131.0	132.2
24-h DBP														
50th	65.6	65.9	66.1	66.4	66.6	66.9	67.1	67.2	67.3	67.5	67.6	67.8	68.0	68.2
75th	69.7	69.9	70.2	70.4	70.6	70.8	71.0	71.1	71.2	71.3	71.5	71.7	71.8	71.9

Table 1
(continued)

b. Normative ABPM values (mmHg) for boys by height (cm)

	Height (cm)													
BP percentile	*120.0*	*125.0*	*130.0*	*135.0*	*140.0*	*145.0*	*150.0*	*155.0*	*160.0*	*165.0*	*170.0*	*175.0*	*180.0*	*185.0*
90th	73.9	74.1	74.2	74.4	74.5	74.7	74.8	74.8	74.9	75.1	75.3	75.4	75.5	75.6
95th	76.7	76.8	76.9	76.9	77.0	77.1	77.1	77.2	77.3	77.5	77.7	77.8	77.9	78.0
99th	82.7	82.5	82.3	82.1	81.9	81.8	81.8	81.8	81.9	82.2	82.5	82.7	82.9	83.0
Daytime DBP														
50th	72.3	72.3	72.2	72.1	72.1	72.1	72.1	72.1	72.2	72.3	72.6	72.8	73.1	73.4
75th	76.5	76.4	76.3	76.2	76.0	76.0	75.9	75.9	76.0	76.2	76.5	76.8	77.2	77.5
90th	80.2	80.1	79.9	79.7	79.5	79.4	79.3	79.3	79.4	79.7	80.0	80.5	80.9	81.3
95th	82.4	82.2	82.0	81.8	81.5	81.4	81.2	81.2	81.3	81.7	82.1	82.6	83.1	83.6
99th	86.5	86.2	85.9	85.6	85.2	85.0	84.8	84.8	85.0	85.4	86.0	86.6	87.3	87.9
Nighttime DBP														
50th	54.3	54.8	55.1	55.5	55.8	56.0	56.2	56.2	56.3	56.5	56.7	56.9	57.1	57.3
75th	57.6	58.2	58.8	59.2	59.6	59.9	60.1	60.2	60.2	60.3	60.5	60.6	60.8	60.9
90th	60.7	61.4	62.1	62.7	63.2	63.5	63.7	63.8	63.8	63.9	63.9	64.0	64.1	64.2
95th	62.6	63.4	64.2	64.8	65.4	65.8	66.0	66.0	66.0	66.0	66.1	66.1	66.1	66.2
99th	66.2	67.2	68.2	69.0	69.7	70.1	70.4	70.4	70.3	70.3	70.2	70.1	70.0	69.9
24-h MAP														
50th	77.5	78.1	78.7	79.3	79.9	80.5	81.1	81.7	82.3	83.1	83.9	84.7	85.5	86.3
75th	81.8	82.4	83.0	83.5	84.1	84.6	85.2	85.9	86.6	87.3	88.1	89.0	89.8	90.7
90th	86.3	86.7	87.2	87.6	88.0	88.5	89.1	89.7	90.3	91.1	91.9	92.7	93.5	94.3
95th	89.3	89.6	89.9	90.2	90.5	90.9	91.4	91.9	92.6	93.3	94.0	94.8	95.6	96.4
99th	95.9	95.7	95.5	95.4	95.4	95.6	95.9	96.3	96.7	97.4	98.0	98.7	99.4	100.1
Daytime MAP														
50th	83.8	84.1	84.3	84.5	84.7	85.0	85.4	85.8	86.4	87.1	88.0	89.0	90.0	91.0
75th	88.5	88.7	88.9	89.0	89.1	89.4	89.6	90.1	90.7	91.6	92.6	93.7	94.9	96.1
90th	92.9	93.0	93.1	93.1	93.1	93.2	93.4	93.8	94.5	95.4	96.5	97.7	99.0	100.3
95th	95.6	95.6	95.6	95.5	95.5	95.5	95.7	96.0	96.7	97.7	98.8	100.1	101.4	102.8
99th	101.0	100.7	100.5	100.2	99.9	99.7	99.8	100.1	100.8	101.7	102.9	104.3	105.7	107.1
Nighttime MAP														
50th	66.8	67.6	68.3	69.0	69.6	70.1	70.6	71.2	71.9	72.7	73.6	74.5	75.4	76.2
75th	71.0	71.9	72.7	73.4	73.9	74.4	74.9	75.4	76.0	76.8	77.6	78.3	79.1	79.8
90th	75.9	76.6	77.3	77.9	78.3	78.6	78.9	79.2	79.7	80.3	80.9	81.5	82.1	82.7
95th	79.5	80.0	80.5	80.9	81.2	81.3	81.4	81.5	81.9	82.3	82.8	83.3	83.8	84.3
99th	88.4	88.1	87.8	87.6	87.2	86.7	86.3	86.0	86.0	86.1	86.3	86.5	86.8	87.0

c. Normative ABPM values (mmHg) for girls by age (years)

	Age (years)											
BP percentile	*5.0*	*6.0*	*7.0*	*8.0*	*9.0*	*10.0*	*11.0*	*12.0*	*13.0*	*14.0*	*15.0*	*16.0*
24-h SBP												
50th	102.8	104.1	105.3	106.5	107.6	108.7	109.7	110.7	111.8	112.8	113.8	114.8
75th	107.8	109.1	110.4	111.5	112.6	113.6	114.7	115.7	116.7	117.6	118.4	119.2

Table 1
(continued)

	c. Normative ABPM values (mmHg) for girls by age (years)											
	Age (years)											
BP percentile	*5.0*	*6.0*	*7.0*	*8.0*	*9.0*	*10.0*	*11.0*	*12.0*	*13.0*	*14.0*	*15.0*	*16.0*
90th	112.3	113.7	115.0	116.1	117.2	118.2	119.2	120.2	121.2	121.9	122.6	123.2
95th	114.9	116.4	117.7	118.9	120.0	121.1	122.1	123.0	123.9	124.5	125.0	125.6
99th	119.9	121.5	123.0	124.3	125.5	126.5	127.5	128.4	129.0	129.5	129.7	130.0
Daytime SBP												
50th	108.4	109.5	110.6	111.5	112.4	113.3	114.2	115.3	116.4	117.5	118.6	119.6
75th	113.8	114.9	115.9	116.8	117.6	118.5	119.5	120.6	121.7	122.6	123.5	124.3
90th	118.3	119.5	120.6	121.5	122.4	123.3	124.3	125.3	126.4	127.2	127.9	128.5
95th	120.9	122.2	123.3	124.3	125.2	126.2	127.2	128.2	129.2	129.9	130.4	130.9
99th	125.6	127.1	128.4	129.6	130.6	131.7	132.7	133.7	134.5	135.0	135.2	135.4
Nighttime SBP												
50th	94.8	95.6	96.2	96.8	97.5	98.2	99.0	99.7	100.5	101.3	102.0	102.9
75th	100.2	101.1	101.8	102.5	103.2	104.0	104.7	105.2	105.8	106.3	106.8	107.3
90th	105.3	106.3	107.2	108.0	108.8	109.5	110.1	110.4	110.7	110.9	111.0	111.2
95th	108.4	109.6	110.6	111.5	112.3	113.0	113.5	113.6	113.7	113.6	113.5	113.5
99th	114.5	116.0	117.3	118.4	119.3	119.9	120.1	119.8	119.4	118.8	118.2	117.8
24-h DBP												
50th	65.5	65.6	65.8	65.9	66.0	66.2	66.4	66.6	67.0	67.2	67.5	67.7
75th	68.9	69.1	69.2	69.3	69.5	69.8	70.0	70.4	70.8	71.1	71.2	71.4
90th	72.1	72.2	72.3	72.4	72.6	72.9	73.2	73.7	74.1	74.4	74.6	74.7
95th	74.0	74.1	74.2	74.2	74.4	74.7	75.1	75.6	76.1	76.4	76.6	76.7
99th	77.6	77.6	77.6	77.6	77.7	78.0	78.4	79.1	79.7	80.1	80.4	80.5
Daytime DBP												
50th	72.6	72.6	72.4	72.2	72.0	71.8	71.8	72.1	72.4	72.8	73.2	73.5
75th	76.7	76.6	76.5	76.3	76.0	75.9	75.9	76.2	76.5	76.8	77.0	77.2
90th	80.2	80.2	80.0	79.8	79.5	79.3	79.4	79.6	80.0	80.2	80.3	80.3
95th	82.3	82.2	82.1	81.8	81.5	81.3	81.4	81.6	82.0	82.2	82.2	82.1
99th	86.1	86.0	85.8	85.5	85.2	85.0	85.0	85.3	85.6	85.7	85.6	85.4
Nighttime DBP												
50th	56.4	55.9	55.5	55.1	54.8	54.6	54.3	54.2	54.3	54.5	54.9	55.3
75th	61.1	60.6	60.1	59.7	59.4	59.2	58.9	58.7	58.7	58.7	58.8	59.1
90th	65.6	65.1	64.6	64.1	63.8	63.7	63.4	63.1	62.9	62.8	62.8	62.8
95th	68.5	67.9	67.4	66.9	66.6	66.5	66.2	65.9	65.6	65.4	65.3	65.2
99th	74.2	73.6	72.9	72.4	72.2	72.0	71.8	71.4	71.1	70.7	70.3	70.0
24-h MAP												
50th	77.5	78.0	78.4	78.8	79.2	79.6	80.2	80.9	81.5	82.2	82.7	83.0
75th	81.2	81.7	82.1	82.5	82.9	83.3	84.0	84.7	85.4	86.0	86.5	86.8
90th	84.6	85.0	85.4	85.7	86.1	86.5	87.1	87.9	88.6	89.2	89.7	89.9
95th	86.6	87.0	87.3	87.6	87.9	88.3	88.9	89.7	90.5	91.0	91.5	91.7
99th	90.5	90.8	90.9	91.0	91.2	91.6	92.2	93.0	93.7	94.2	94.6	94.8
Daytime MAP												
50th	83.7	83.9	84.0	84.1	84.2	84.4	84.7	85.2	85.9	86.5	87.1	87.7
75th	88.2	88.3	88.4	88.4	88.4	88.5	88.9	89.4	90.1	90.8	91.4	91.9

Table 1
(continued)

c. Normative ABPM values (mmHg) for girls by age (years)

	Age (years)											
BP percentile	*5.0*	*6.0*	*7.0*	*8.0*	*9.0*	*10.0*	*11.0*	*12.0*	*13.0*	*14.0*	*15.0*	*16.0*
90th	92.2	92.2	92.2	92.1	92.0	92.1	92.4	93.0	93.6	94.3	94.8	95.4
95th	94.6	94.5	94.4	94.2	94.1	94.2	94.4	95.0	95.6	96.2	96.8	97.3
99th	99.0	98.7	98.5	98.2	97.9	97.9	98.1	98.6	99.2	99.7	100.2	100.7
Nighttime MAP												
50th	68.7	68.8	68.8	68.8	68.9	69.1	69.3	69.6	70.1	70.6	71.2	71.8
75th	73.0	73.1	73.1	73.2	73.4	73.6	73.8	74.1	74.5	74.9	75.4	75.9
90th	76.9	77.0	77.1	77.2	77.4	77.6	77.8	78.0	78.3	78.6	78.9	79.3
95th	79.2	79.4	79.6	79.7	79.8	80.1	80.2	80.3	80.5	80.7	80.9	81.2
99th	83.8	84.1	84.2	84.3	84.5	84.6	84.7	84.6	84.6	84.6	84.6	84.7

d. Normative ABPM values (mmHg) for girls by height (cm)

	Height (cm)											
BP percentile	*120.0*	*125.0*	*130.0*	*135.0*	*140.0*	*145.0*	*150.0*	*155.0*	*160.0*	*165.0*	*170.0*	*175.0*
24-h SBP												
50th	104.0	105.0	106.0	106.8	107.6	108.7	109.9	111.2	112.4	113.7	115.0	116.4
75th	108.2	109.3	110.3	111.2	112.1	113.2	114.6	115.9	117.0	118.0	119.2	120.4
90th	112.0	113.2	114.3	115.3	116.2	117.4	118.7	120.0	121.0	121.8	122.8	123.8
95th	114.3	115.6	116.7	117.7	118.7	119.9	121.2	122.5	123.3	124.1	124.9	125.8
99th	118.8	120.1	121.3	122.4	123.4	124.6	126.0	127.1	127.7	128.2	128.8	129.3
Daytime SBP												
50th	110.0	110.5	111.0	111.6	112.2	113.1	114.3	115.6	117.0	118.3	119.8	121.2
75th	114.4	115.0	115.7	116.3	117.0	118.1	119.4	120.7	121.9	123.1	124.2	125.3
90th	118.2	119.0	119.7	120.4	121.3	122.5	123.9	125.2	126.4	127.3	128.1	128.9
95th	120.4	121.3	122.1	122.9	123.8	125.1	126.5	127.9	129.1	129.8	130.5	131.0
99th	124.5	125.5	126.4	127.4	128.5	129.9	131.5	133.0	134.0	134.5	134.8	135.0
Nighttime SBP												
50th	95.0	95.7	96.4	96.9	97.5	98.1	98.9	100.0	101.1	102.2	103.4	104.6
75th	99.4	100.3	101.2	101.9	102.6	103.4	104.4	105.5	106.4	107.3	108.2	109.2
90th	103.3	104.4	105.5	106.5	107.5	108.5	109.5	110.5	111.2	111.8	112.4	113.1
95th	105.6	106.9	108.1	109.3	110.4	111.6	112.7	113.6	114.1	114.4	114.8	115.3
99th	109.8	111.5	113.1	114.7	116.2	117.7	118.9	119.5	119.6	119.4	119.3	119.4
24-h DBP												
50th	65.9	65.9	66.0	66.1	66.2	66.3	66.5	66.7	67.0	67.4	68.0	68.6
75th	68.6	68.9	69.2	69.5	69.8	70.1	70.4	70.6	70.7	71.0	71.3	71.6
90th	70.9	71.4	71.9	72.4	72.9	73.4	73.8	74.0	74.1	74.2	74.4	74.5
95th	72.2	72.8	73.4	74.1	74.7	75.3	75.7	76.0	76.1	76.2	76.2	76.2
99th	74.6	75.3	76.2	77.1	77.9	78.7	79.3	79.7	79.9	79.9	79.9	79.7
Daytime DBP												
50th	73.2	72.8	72.4	72.1	71.8	71.7	71.8	72.0	72.4	73.1	73.9	74.8
75th	76.9	76.6	76.4	76.2	76.1	76.1	76.1	76.2	76.4	76.8	77.3	77.8

Table 1
(continued)

	d. Normative ABPM values (mmHg) for girls by height (cm)											
	Height (cm)											
BP percentile	*120.0*	*125.0*	*130.0*	*135.0*	*140.0*	*145.0*	*150.0*	*155.0*	*160.0*	*165.0*	*170.0*	*175.0*
90th	80.1	79.9	79.8	79.8	79.7	79.8	79.9	79.9	79.9	80.0	80.2	80.5
95th	81.9	81.8	81.8	81.8	81.9	82.0	82.0	82.0	82.0	81.9	82.0	82.0
99th	85.3	85.3	85.4	85.6	85.8	85.9	86.0	85.9	85.7	85.4	85.2	84.9
Nighttime DBP												
50th	55.4	55.3	55.1	54.8	54.6	54.4	54.3	54.4	54.6	54.9	55.1	55.4
75th	59.5	59.5	59.4	59.3	59.1	58.9	58.8	58.7	58.8	58.9	61.0	59.3
90th	63.1	63.3	63.4	63.4	63.3	63.1	63.0	62.9	62.9	62.9	66.9	63.1
95th	65.2	65.5	65.7	65.8	65.8	65.7	65.6	65.5	65.5	65.5	70.8	65.5
99th	69.1	69.6	70.1	70.4	70.6	70.8	70.8	70.7	70.7	70.6	79.0	70.4
24-h MAP												
50th	77.2	77.8	78.3	78.7	79.2	79.7	80.2	80.8	81.5	82.3	83.1	84.0
75th	80.6	81.2	81.8	82.4	82.9	83.5	84.1	84.7	85.3	85.9	86.6	87.4
90th	83.6	84.2	84.9	85.5	86.1	86.7	87.3	87.9	88.4	88.9	89.5	90.1
95th	85.3	86.0	86.7	87.4	88.0	88.6	89.2	89.7	90.2	90.6	91.1	91.7
99th	88.5	89.2	89.9	90.6	91.3	91.9	92.5	93.0	93.3	93.6	94.0	94.5
Daytime MAP												
50th	83.3	83.7	84.0	84.1	84.3	84.5	84.9	85.5	86.2	87.0	88.0	88.9
75th	87.4	87.9	88.2	88.5	88.7	88.9	89.3	89.8	90.3	90.9	91.6	92.2
90th	90.9	91.5	91.9	92.2	92.4	92.7	93.0	93.4	93.7	94.1	94.5	94.9
95th	92.9	93.6	94.0	94.4	94.6	94.9	95.1	95.4	95.6	95.8	96.1	96.4
99th	96.6	97.4	97.9	98.3	98.6	98.8	99.0	99.0	99.0	99.0	99.0	99.1
Nighttime MAP												
50th	68.0	68.2	68.4	68.5	68.7	69.0	69.3	69.8	70.4	71.2	72.0	72.8
75th	72.6	72.7	72.9	73.0	73.2	73.5	73.9	74.3	74.8	75.4	76.1	76.9
90th	76.8	76.9	77.0	77.2	77.4	77.7	78.0	78.3	78.6	79.1	79.6	80.3
95th	79.5	79.4	79.6	79.7	79.9	80.2	80.4	80.6	80.8	81.2	81.6	82.2
99th	84.6	84.4	84.5	84.6	84.8	85.0	85.0	85.0	85.0	85.0	85.3	85.6

Adapted from Wühl et al. *(25)*, with permission.

The recommended frequency for ABPM measurements is 15–20 min during daytime and 30–60 min during nighttime, resulting in at least 40–50 readings within 24 h. A low frequency of measurements is more comfortable for the patient but limits the validity of the individual profile. For analyses of blood pressure rhythmicity (ultradian rhythms) intervals of 15–20 min during daytime and of 20–30 min during nighttime are recommended *(8)*.

The ABPM recording should be edited for outliers by visual inspection of the profile. Values outside preset cutoffs (e.g., systolic BP < 60 or > 220 mmHg, diastolic BP < 35 or > 120 mmHg, heart rate < 40 or > 180 bpm, pulse pressure < 40 or > 120 mmHg) should be excluded a priori by the ABPM software program *(17)*.

All patients should be instructed to fill in a diary on physical activity, rest and sleeping times, and drug intake. This is important to account for different levels of physical activity

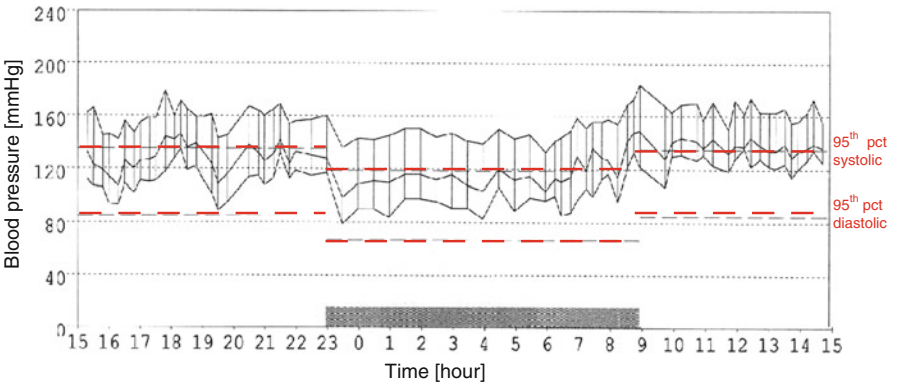

Fig. 1. Example of an ABPM profile in a child with marked systolic and diastolic hypertension. The dipping pattern is conserved (>10% difference between mean daytime and mean nighttime BP). The systolic and diastolic load (percent of BP measurements above the 95th percentile) is 100%.

during BP recording and the effect of antihypertensive medication. Daytime and nighttime (awake and sleeping periods) should be analyzed as reported in the patient's diary *(27,28)*. If information is not available alternatively the time period from 8 am to 8 pm might be chosen for daytime and from midnight to 6 am for nighttime BP evaluation. This approach discards readings obtained during transition times (i.e., 6–8 am and 10 pm to midnight) from the analysis *(24)*. Preliminary data suggest that actual sleeping and waking times determined from an actigraph, a wrist device that senses motion, may be superior to patient-initiated diary entry *(29)*.

Physical activity influences the success of BP measurements and BP itself. Simultaneous recording of activity by actigraphs shows that reliable and reproducible ABPM is feasible and that activity increases SBP and DBP by up to 10 mmHg *(2)*. It is recommended that children undergoing ABPM should continue normal activities except contact sports, vigorous exercise, and swimming. During individual measurements the arm should be held still to avoid erroneous readings.

Applying the Device

The personnel applying the ABPM monitors should be fully trained on their maintenance, application, and function. The cuffs should be laundered regularly; some manufacturers sell single-use covers for the BP cuffs. The device itself should be regularly cleaned with a wiping disinfectant.

Parents and patients should be informed how to operate the monitor (e.g., stop a reading, turn off, or restart the device). Although removal of the monitor is not recommended, if absolutely necessary, the device should be removed immediately after a reading (to reduce the number of missed readings) and reapplied as soon as possible. Contact of the electronic device with water must be avoided.

Serious adverse events have not been reported in children; however, mild sleep disturbances, petechiae, or bruises have been documented *(30)*. Contraindications to ABPM may include atrial fibrillation, coagulation disorders, and, for some brands of equipment, latex allergy.

The accuracy and precision of the devices should be checked by simultaneous measurements with a sphygmomanometer at the beginning of each test period. The average difference between the mean of three clinic and three ABPM measurements should be less than 5 mmHg to consider adequate calibration.

The cuff should be applied to the non-dominant arm, in hemodialysis patients to the non-fistula arm.

Normative Data

Comparison with appropriate normative data stratified by gender and age or height is essential for a meaningful interpretation of ABPM findings in the pediatric setting (see Table 1).

In childhood, BP is strongly influenced by body dimensions *(3,16,24,26,31–34)*. In addition, changes in body composition during puberty have profound gender-specific effects on BP. Furthermore, the level, timing, and duration of physical activity are markedly age and gender dependent. For example, median 24-h systolic BP increases across childhood by almost 19 mmHg in boys and 12 mmHg in girls *(25)*. Up to 11 years of age or 140 cm of height, median values are virtually identical in boys and girls. During puberty systolic BP increases more steeply in boys, resulting in a median difference of 8.4 mmHg at the age of 16 years. These differences are equally marked during daytime and nighttime *(25)*.

In contrast to the marked increase in systolic BP, diastolic BP increases only minimally with age during childhood. The median increase in median 24-h diastolic BP over time was 3.3 and 2.2 mmHg in boys and girls, respectively *(25)*. This finding is in contrast to reference data for casual BP measurements *(32,35,36)*. In addition, the age-related increase in systolic BP is less marked than in casual BP reference studies. These discrepancies might be explained by a decreasing prevalence of the white coat phenomenon across childhood. However, technical artifacts, such as age-dependent differences in cuff size relative to upper arm circumference between manual and ABPM devices, cannot be completely ruled out. It is also possible that age-related differences in diastolic BP might be related to difficulties in defining diastolic BP by Korotkoff phases IV and V by auscultatory BP measurements or to the use of invalidated algorithms implemented in ABPM devices. However, even using auscultatory measurements, no systematic increase of mean diastolic BP with age was observed in a recent ABPM study assessing a large number of children aged 6–16 years, whereas systolic BP was clearly age dependent *(23)*.

An overview on published ABPM normative data sets is given in Table 2. Up to date, few large cross-sectional ABPM studies have been performed in healthy controls. For all these studies the cutoff values for the normal range were defined by the 95th percentile of the BP distribution in healthy children. It should be recognized that ABPM BP values measured with an oscillometric device tend to be higher than resting BP values obtained by auscultation. This difference will lead to a difference in the prevalence of hypertension if the higher ambulatory norms *(24,25)* are used as reference compared to the lower, resting casual BP normative data (4th report). In a study by Sorof, white coat hypertension was diagnosed in only 31% of patients using the ambulatory criteria, whereas applying the lower casual BP cutoffs would result in 59% being diagnosed with white coat hypertension *(37)*.

For casual BP a staging system was introduced (JNC7 *(13)* and 4th report *(16)*). A similar staging scheme was suggested for ABPM BP levels in children including mean ABPM levels and the calculated BP load *(38)* (see Table 3). BP load is defined as the percentage of valid ambulatory BP measures above a set threshold value, such as the 95th percentile of

Table 2
Published Normative ABPM Data Sets

Authors	*No. of subjects*	*Age range studied (years)*	*Method*	*Successful exams (%)*	*Successful readings (%)*
Harshfield et al. *(34)*	300	10–18	ausc + osc	84	85–90
Lurbe et al. *(26,64)*	333	3–18	osc	84	89.8
O'Sullivan et al. *(23)*	1121	6–16	ausc + osc	99.7	>95
Reichert et al. *(3)*	564	9–13	ausc + osc	95	64
Soergel et al. *(24)*	1245	5–21	osc	98.9	92.7
Wühl et al. *(25)*	949[a]	5–20	osc	[a]	[a]
Gellermann et al. *(19)*	61	3–6	osc	77	46–58
Varda and Gregoric *(18)*	97	0.1–2.5	osc	87	75

Osc, oscillometric device; ausc, auscultatory device.
[a]Analysis of the data set from Soergel et al. *(24)* by the LMS method *(47)*. Only complete 24-h profiles without significant gaps were eligible for this analysis.

Table 3
Staging Scheme for Ambulatory Blood Pressure Levels in Children

Staging	*Clinic BP*[a]	*Mean ambulatory systolic BP*[b]	*SBP load (%)*
Normal BP	<95th percentile	<95th percentile	<25
White coat hypertension	>95th percentile	<95th percentile	<25
Masked hypertension	<95th percentile	>95th percentile	>25
High normal BP	>95th percentile	<95th percentile	25–50
Ambulatory hypertension	>95th percentile	>95th percentile	25–50
Severe ambulatory hypertension (at risk for end-organ damage)	>95th percentile	>95th percentile	>50

BP, blood pressure.
[a]Based on the National High Blood Pressure Education Program data (4th report) *(16)*.
[b]Based on normative ABPM values *(24,25)*.
Modified from Lurbe et al. *(38)*, with permission.

BP for gender and age or height *(39)*. The load can be assessed for the entire 24-h period or for the awake and asleep periods separately. Loads in excess of 25–30% are considered elevated *(40)*. Loads in excess of 50% were predictive of LVH in one pediatric study *(41)*.

ABPM also allows the evaluation of nocturnal BP dipping. Normal dipping is generally defined as a nocturnal decline of mean systolic and diastolic ABPM level by at least 10%.

The non-dipping phenomenon contributes to the overall renal and cardiovascular risk of an individual *(42–44)*. The cardiovascular mortality risk attributable to non-dipping is independent of the absolute 24-h blood pressure load *(45)*. Blunted nocturnal dipping has been associated with nephropathy in patients with type 1 *(46)* and 2 diabetes mellitus *(28)* and may be an early marker for impaired renal function.

The scientific application of pediatric ABPM reference data in parametric statistical procedures is compromised by the skewed distribution of BP in childhood. This problem has been largely solved by introduction of the LMS normalization method of Cole and Green *(47)*, which transforms skewed BP values into normally distributed standard deviation scores (SDS) *(25)*. In brief, the LMS method describes the distribution of a measurement Y by its median (M), the coefficient of variation (S), and a measure of skewness (L) required to transform the data to normality. Estimates for these parameters are obtained by applying a maximum-likelihood curve-fitting algorithm to the original data plotted over the independent variable of interest, in this case either age or height. The resulting estimates of L, M, and S can be used to construct percentiles ($C_{\text{alpha}}(t)$) by the equation: $C_{\text{alpha}}(t) = M(t)[1 + L(t) \times S(t) \times z_{\text{alpha}}]^{1/L(t)}$, where $M(t)$, $L(t)$, $S(t)$, and $C_{\text{alpha}}(t)$ indicate the corresponding values of each parameter at age (or height) t. z_{alpha} is the appropriate normal equivalent deviate (e.g., for alpha = 97%, $z_{\text{alpha}} = 1.88$).

This equation can be rearranged to convert an individual child's BP value to an exact standard deviation score (SDS):

$\text{SDS} = [(Y/M(t))^{L(t)} - 1]/(L(t) \times S(t))$, where Y is the child's individual systolic, diastolic, mean arterial BP, or heart rate value, and $L(t)$, $M(t)$, and $S(t)$ are the gender-specific values of L, M, and S interpolated for the child's age or height.

Age-, gender-, and height-specific L, M, and S reference values for mean 24-h, daytime, and nighttime systolic, diastolic, and mean arterial pressure have been provided *(25)* (Table 4).

Advantages of ABPM vs. Home BP or Casual BP Measurements

Self-monitoring of BP (home BP) has been suggested as an alternative to ABPM in adults *(48)*. Home BP measurements appear to be a valuable addition to casual BP also in children *(49)*. Home BP measurements agree with ABPM more closely and more consistently over the whole range of BP *(50)*. The combination of home and casual BP yields a higher degree of diagnostic specificity than casual BP alone. However, the information obtained from home BP measurements cannot substitute for ABPM: in children, the maximum diagnostic sensitivity reached by combined home and casual BP is only 81%, thus one out of four children diagnosed as hypertensive by ABPM would still be missed *(50)*. Moreover, the range of agreement of home BP with ABPM, albeit narrower than that of casual BP, is unacceptably wide. Finally, alterations of nocturnal BP regulation or hypertension, which have a high prevalence in children with chronic kidney disease, cannot be assessed by any daytime BP measurement.

Variability of Blood Pressure

ABPM provides information not only on daytime and nighttime blood pressure patterns but also on BP variability. Linear analyses, such as dividing the 24-h period into day and

Table 4
LMS Reference Values of Mean 24-h, Daytime, and Nighttime Systolic, Diastolic, and Mean Arterial Pressure Relative to Age and Height in Boys and Girls

Boys

		Systolic BP									Diastolic BP									MAP								
		24 h			Day			Night			24 h			Day			Night			24 h			Day			Night		
Age	N	L	M	S	L	M	S	L	M	S	L	M	S	L	M	S	L	M	S	L	M	S	L	M	S	L	M	S
5.0	11	−2.205	104.6	0.058	−0.862	111.1	0.059	−1.929	95.0	0.062	−0.661	65.3	0.076	1.477	72.1	0.075	−2.245	55.0	0.086	−2.063	76.9	0.071	−0.132	83.5	0.069	−2.191	66.7	0.078
5.5	11	−2.066	105.1	0.059	−0.807	111.3	0.060	−1.793	95.3	0.065	−0.502	65.5	0.076	1.505	72.2	0.076	−2.065	55.1	0.089	−1.918	77.4	0.071	−0.069	83.8	0.070	−2.074	67.2	0.079
6.0	11	−1.927	105.5	0.060	−0.751	111.5	0.061	−1.658	95.5	0.067	−0.342	65.7	0.077	1.533	72.4	0.077	−1.884	55.3	0.092	−1.772	77.9	0.071	−0.007	84.1	0.071	−1.955	67.7	0.081
6.5	14	−1.786	105.9	0.061	−0.691	111.7	0.062	−1.522	95.8	0.070	−0.178	65.9	0.077	1.558	72.4	0.078	−1.702	55.4	0.095	−1.610	78.3	0.071	0.060	84.3	0.072	−1.826	68.1	0.082
7.0	15	−1.646	106.3	0.062	−0.631	111.9	0.063	−1.386	96.1	0.073	−0.014	66.1	0.077	1.583	72.5	0.079	−1.520	55.5	0.098	−1.447	78.7	0.071	0.127	84.5	0.073	−1.696	68.6	0.084
7.5	21	−1.503	106.6	0.063	−0.567	112.0	0.064	−1.251	96.4	0.076	0.144	66.2	0.077	1.599	72.5	0.080	−1.338	55.6	0.100	−1.262	79.0	0.072	0.199	84.7	0.074	−1.544	68.9	0.085
8.0	22	−1.360	107.0	0.065	−0.503	112.2	0.065	−1.116	96.6	0.078	0.301	66.3	0.078	1.614	72.5	0.081	−1.155	55.7	0.102	−1.078	79.3	0.072	0.272	84.8	0.076	−1.393	69.2	0.086
8.5	22	−1.220	107.4	0.066	−0.440	112.4	0.066	−0.984	97.0	0.080	0.441	66.4	0.078	1.620	72.4	0.082	−0.982	55.7	0.104	−0.870	79.5	0.073	0.353	84.8	0.077	−1.220	69.5	0.087
9.0	21	−1.086	107.7	0.067	−0.381	112.6	0.067	−0.856	97.3	0.081	0.574	66.5	0.078	1.622	72.3	0.083	−0.813	55.8	0.105	−0.651	79.7	0.073	0.442	84.9	0.078	−1.040	69.7	0.088
9.5	23	−0.968	108.2	0.068	−0.326	112.9	0.068	−0.733	97.7	0.082	0.688	66.5	0.079	1.621	72.1	0.083	−0.655	55.8	0.105	−0.409	79.9	0.074	0.552	84.9	0.078	−0.843	69.8	0.089
10.0	19	−0.866	108.8	0.069	−0.276	113.4	0.069	−0.616	98.1	0.083	0.786	66.6	0.079	1.614	72.1	0.083	−0.505	55.8	0.106	−0.146	80.2	0.075	0.682	85.0	0.079	−0.631	70.0	0.090
10.5	27	−0.783	109.6	0.069	−0.229	114.1	0.070	−0.503	98.7	0.084	0.865	66.7	0.079	1.598	72.0	0.083	−0.365	55.8	0.106	0.139	80.5	0.075	0.832	85.1	0.079	−0.398	70.2	0.090
11.0	25	−0.706	110.4	0.070	−0.177	114.9	0.071	−0.391	99.4	0.084	0.932	66.9	0.079	1.576	72.0	0.083	−0.229	55.9	0.105	0.443	80.8	0.076	0.998	85.3	0.080	−0.147	70.5	0.091
11.5	36	−0.627	111.5	0.071	−0.115	115.9	0.072	−0.280	100.2	0.084	0.981	67.0	0.080	1.544	72.0	0.083	−0.097	55.9	0.105	0.774	81.2	0.077	1.183	85.6	0.080	0.133	70.8	0.091
12.0	27	−0.540	112.6	0.072	−0.041	117.0	0.072	−0.171	101.2	0.084	1.017	67.2	0.080	1.505	72.0	0.083	0.031	56.0	0.104	1.119	81.7	0.077	1.378	85.9	0.081	0.437	71.2	0.091
12.5	35	−0.441	113.8	0.072	0.041	118.2	0.073	−0.065	102.2	0.084	1.040	67.3	0.080	1.460	72.1	0.083	0.154	56.1	0.104	1.470	82.1	0.078	1.569	86.3	0.081	0.761	71.6	0.090
13.0	21	−0.324	115.1	0.072	0.132	119.5	0.073	0.040	103.4	0.084	1.050	67.4	0.080	1.407	72.2	0.083	0.270	56.3	0.104	1.822	82.7	0.078	1.755	86.8	0.082	1.097	72.1	0.089
13.5	30	−0.181	116.4	0.073	0.235	120.9	0.073	0.144	104.6	0.083	1.047	67.6	0.080	1.347	72.3	0.083	0.378	56.4	0.103	2.173	83.2	0.078	1.937	87.4	0.082	1.436	72.6	0.088
14.0	16	−0.018	117.8	0.073	0.348	122.3	0.073	0.248	105.8	0.083	1.036	67.7	0.080	1.279	72.5	0.082	0.483	56.5	0.102	2.525	83.8	0.078	2.117	88.0	0.083	1.777	73.1	0.086
14.5	19	0.157	119.2	0.073	0.469	123.8	0.073	0.349	107.1	0.082	1.019	67.9	0.079	1.203	72.7	0.082	0.588	56.7	0.101	2.874	84.4	0.078	2.291	88.7	0.083	2.122	73.6	0.084
15.0	11	0.338	120.6	0.072	0.595	125.3	0.073	0.448	108.3	0.082	1.000	68.1	0.079	1.123	73.0	0.082	0.694	56.8	0.100	3.222	85.1	0.078	2.464	89.4	0.083	2.469	74.0	0.082
15.5	9	0.522	122.0	0.072	0.723	126.8	0.073	0.545	109.6	0.081	0.980	68.4	0.079	1.040	73.2	0.083	0.801	57.0	0.099	3.571	85.7	0.077	2.635	90.1	0.084	2.816	74.5	0.080
16.0	18	0.706	123.4	0.072	0.851	128.2	0.073	0.641	110.9	0.080	0.959	68.6	0.079	0.957	73.5	0.083	0.908	57.1	0.098	3.919	86.4	0.077	2.806	90.8	0.084	3.164	74.9	0.077

		Systolic BP									Diastolic BP									MAP								
		24 h			Day			Night			24 h			Day			Night			24h			Day			Night		
Height	N	L	M	S	L	M	S	L	M	S	L	M	S	L	M	S	L	M	S	L	M	S	L	M	S	L	M	S
120	31	−1.123	104.5	0.063	−1.291	110.8	0.069	−0.053	93.6	0.077	−1.177	65.6	0.087	1.345	72.3	0.087	0.440	54.3	0.089	−1.747	77.5	0.076	0.135	83.8	0.081	−2.736	66.8	0.084
125	25	−0.991	105.3	0.064	−1.007	111.1	0.069	−0.314	94.6	0.079	−0.957	65.9	0.087	1.436	72.3	0.086	0.430	54.8	0.092	−1.352	78.1	0.076	0.368	84.1	0.080	−2.305	67.6	0.085
130	25	−0.856	106.2	0.065	−0.710	111.5	0.069	−0.570	95.6	0.080	−0.733	66.1	0.087	1.531	72.2	0.086	0.421	55.1	0.095	−0.951	78.7	0.076	0.604	84.3	0.079	−1.867	68.3	0.086
135	44	−0.709	107.2	0.066	−0.380	112.0	0.068	−0.807	96.7	0.081	−0.511	66.4	0.086	1.629	72.1	0.085	0.410	55.5	0.098	−0.547	79.3	0.076	0.844	84.5	0.078	−1.411	69.0	0.087
140	50	−0.556	108.3	0.066	−0.075	112.7	0.067	−0.997	97.9	0.082	−0.322	66.6	0.086	1.711	72.1	0.083	0.398	55.8	0.100	−0.148	79.9	0.075	1.083	84.7	0.077	−0.932	69.6	0.087
145	48	−0.406	109.5	0.067	0.117	113.7	0.067	−1.106	99.0	0.082	−0.183	66.9	0.085	1.763	72.1	0.082	0.391	56.0	0.101	0.235	80.5	0.076	1.309	85.0	0.076	−0.427	70.1	0.087
150	43	−0.275	110.9	0.067	0.125	115.1	0.067	−1.126	100.1	0.081	−0.107	67.1	0.084	1.777	72.1	0.081	0.395	56.2	0.101	0.589	81.1	0.076	1.509	85.4	0.076	0.092	70.6	0.087
155	32	−0.155	112.5	0.067	−0.031	116.8	0.066	−1.068	101.3	0.081	−0.110	67.2	0.083	1.740	72.1	0.080	0.413	56.2	0.101	0.914	81.7	0.076	1.680	85.8	0.076	0.620	71.2	0.086
160	39	−0.017	114.2	0.067	−0.251	118.6	0.067	−0.948	102.6	0.080	−0.189	67.3	0.083	1.650	72.2	0.081	0.442	56.3	0.100	1.217	82.3	0.077	1.829	86.4	0.076	1.159	71.9	0.085
165	29	0.154	116.1	0.066	−0.431	120.6	0.068	−0.795	104.1	0.079	−0.324	67.5	0.082	1.509	72.3	0.081	0.487	56.5	0.099	1.509	83.1	0.077	1.963	87.1	0.078	1.706	72.7	0.084
170	28	0.378	118.0	0.066	−0.463	122.6	0.069	−0.626	105.6	0.079	−0.479	67.6	0.081	1.329	72.6	0.082	0.556	56.7	0.097	1.805	83.9	0.077	2.092	88.0	0.080	2.269	73.6	0.082
175	31	0.651	119.7	0.064	−0.373	124.4	0.069	−0.451	107.2	0.078	−0.635	67.8	0.080	1.136	72.8	0.082	0.647	56.9	0.096	2.110	84.7	0.078	2.226	89.0	0.082	2.843	74.5	0.080
180	20	0.942	121.5	0.063	−0.244	126.2	0.069	−0.277	108.7	0.078	−0.785	68.0	0.078	0.939	73.1	0.083	0.755	57.1	0.094	2.423	85.5	0.078	2.364	90.0	0.084	3.425	75.4	0.078
185	19	1.240	123.2	0.061	−0.098	128.0	0.069	−0.100	110.2	0.078	−0.932	68.2	0.077	0.741	73.4	0.083	0.871	57.3	0.093	2.737	86.3	0.079	2.503	91.0	0.087	4.010	76.2	0.075

Table 4 (continued)

Girls

		Systolic BP									Diastolic BP									MAP								
		24 h			Day			Night			24 h			Day			Night			24 h			Day			Night		
Age	N	L	M	S	L	M	S	L	M	S	L	M	S	L	M	S	L	M	S	L	M	S	L	M	S	L	M	S
5.0	14	1.362	102.8	0.073	2.507	108.4	0.077	0.144	94.8	0.082	0.646	65.5	0.078	1.670	72.6	0.085	0.122	56.4	0.120	0.487	77.2	0.070	1.277	83.7	0.080	0.507	68.7	0.090
5.5	15	1.174	103.4	0.073	2.274	109.0	0.075	0.052	95.2	0.082	0.773	65.5	0.078	1.717	72.6	0.085	0.120	56.2	0.120	0.675	77.5	0.070	1.371	83.8	0.079	0.528	68.8	0.090
6.0	15	0.987	104.1	0.072	2.041	109.5	0.074	−0.040	95.6	0.083	0.900	65.6	0.078	1.765	72.6	0.085	0.119	55.9	0.119	0.864	77.8	0.070	1.465	83.9	0.079	0.549	68.8	0.091
6.5	17	0.811	104.7	0.071	1.819	110.1	0.073	−0.123	95.9	0.083	1.025	65.7	0.078	1.813	72.5	0.085	0.123	55.7	0.119	1.051	78.0	0.070	1.560	84.0	0.078	0.579	68.8	0.092
7.0	17	0.648	105.3	0.070	1.610	110.6	0.073	−0.194	96.2	0.083	1.148	65.8	0.078	1.861	72.4	0.085	0.129	55.5	0.119	1.239	78.2	0.071	1.656	84.0	0.078	0.617	68.8	0.092
7.5	13	0.503	105.9	0.069	1.417	111.1	0.072	−0.250	96.5	0.084	1.269	65.8	0.079	1.911	72.3	0.086	0.137	55.3	0.120	1.427	78.4	0.071	1.755	84.1	0.077	0.662	68.8	0.093
8.0	12	0.378	106.5	0.069	1.244	111.5	0.071	−0.286	96.8	0.084	1.388	65.9	0.079	1.962	72.2	0.086	0.142	55.1	0.120	1.618	78.6	0.071	1.857	84.1	0.077	0.711	68.8	0.094
8.5	12	0.278	107.0	0.068	1.096	111.9	0.070	−0.298	97.2	0.084	1.503	65.9	0.080	2.015	72.1	0.086	0.143	54.9	0.120	1.811	78.8	0.071	1.961	84.1	0.077	0.765	68.9	0.095
9.0	12	0.199	107.6	0.067	0.969	112.4	0.070	−0.289	97.5	0.084	1.611	66.0	0.080	2.066	72.0	0.086	0.141	54.8	0.121	2.001	79.0	0.071	2.066	84.2	0.076	0.824	68.9	0.095
9.5	22	0.154	108.2	0.066	0.874	112.8	0.069	−0.253	97.9	0.084	1.701	66.1	0.081	2.109	71.9	0.087	0.135	54.7	0.121	2.181	79.2	0.071	2.171	84.3	0.076	0.893	69.0	0.096
10.0	20	0.134	108.7	0.066	0.805	113.3	0.069	−0.197	98.2	0.084	1.775	66.2	0.082	2.146	71.8	0.087	0.125	54.6	0.121	2.352	79.4	0.071	2.274	84.4	0.076	0.970	69.1	0.096
10.5	37	0.151	109.2	0.066	0.775	113.7	0.068	−0.116	98.6	0.084	1.819	66.3	0.083	2.175	71.8	0.087	0.112	54.5	0.121	2.506	79.6	0.072	2.375	84.5	0.076	1.059	69.2	0.097
11.0	31	0.201	109.7	0.065	0.780	114.2	0.068	−0.015	99.0	0.083	1.832	66.4	0.084	2.195	71.8	0.087	0.096	54.3	0.121	2.640	79.9	0.072	2.474	84.7	0.076	1.160	69.3	0.097
11.5	35	0.280	110.2	0.065	0.819	114.7	0.068	0.106	99.3	0.082	1.811	66.5	0.085	2.207	71.9	0.088	0.074	54.2	0.120	2.749	80.2	0.073	2.570	84.9	0.076	1.274	69.4	0.097
12.0	31	0.378	110.7	0.065	0.878	115.3	0.068	0.241	99.7	0.081	1.757	66.6	0.086	2.210	72.1	0.087	0.043	54.2	0.119	2.836	80.5	0.073	2.663	85.2	0.076	1.399	69.6	0.097
12.5	37	0.485	111.3	0.065	0.945	115.8	0.068	0.389	100.1	0.079	1.675	66.8	0.086	2.203	72.2	0.087	0.001	54.2	0.117	2.902	80.9	0.074	2.753	85.5	0.076	1.534	69.8	0.096
13.0	27	0.599	111.8	0.064	1.020	116.4	0.067	0.549	100.5	0.078	1.571	67.0	0.086	2.192	72.4	0.087	−0.051	54.3	0.115	2.957	81.2	0.074	2.843	85.9	0.077	1.676	70.1	0.095
13.5	30	0.722	112.3	0.064	1.107	117.0	0.066	0.720	100.9	0.076	1.453	67.1	0.086	2.179	72.6	0.085	−0.110	54.4	0.112	3.008	81.5	0.074	2.933	86.2	0.076	1.825	70.3	0.094
14.0	20	0.854	112.8	0.063	1.207	117.5	0.065	0.898	101.3	0.074	1.328	67.2	0.085	2.169	72.8	0.084	−0.174	54.5	0.109	3.061	81.9	0.074	3.026	86.5	0.076	1.977	70.6	0.093
14.5	24	0.991	113.3	0.062	1.319	118.1	0.063	1.083	101.6	0.072	1.202	67.4	0.084	2.162	73.0	0.082	−0.243	54.7	0.106	3.121	82.2	0.073	3.122	86.8	0.076	2.132	70.9	0.092
15.0	16	1.129	113.8	0.061	1.435	118.6	0.062	1.269	102.0	0.069	1.075	67.5	0.082	2.158	73.2	0.080	−0.316	54.9	0.102	3.183	82.4	0.073	3.219	87.1	0.076	2.287	71.2	0.090
15.5	12	1.265	114.3	0.059	1.552	119.1	0.061	1.454	102.5	0.067	0.946	67.6	0.081	2.153	73.3	0.078	−0.391	55.1	0.099	3.243	82.7	0.072	3.317	87.4	0.075	2.440	71.5	0.089
16.0	16	1.400	114.8	0.058	1.668	119.6	0.059	1.639	102.9	0.065	0.816	67.7	0.080	2.148	73.5	0.076	−0.467	55.3	0.096	3.302	83.0	0.072	3.415	87.7	0.075	2.593	71.8	0.088

		Systolic BP									Diastolic BP									MAP								
		24 h			Say			Night			24 h			Day			Night			24 h			Day			Night		
Height	N	L	M	S	L	M	S	L	M	S	L	M	S	L	M	S	L	M	S	L	M	S	L	M	S	L	M	S
120	30	0.593	104.0	0.059	2.107	110.0	0.061	1.565	95.0	0.070	2.996	65.9	0.065	1.952	73.2	0.077	1.491	55.4	0.112	1.848	77.2	0.067	2.092	83.3	0.074	0.335	68.0	0.097
125	32	0.553	105.0	0.060	1.947	110.5	0.062	1.184	95.7	0.071	2.790	65.9	0.070	1.915	72.8	0.080	1.276	55.3	0.115	1.976	77.8	0.068	2.039	83.7	0.076	0.410	68.2	0.096
130	27	0.535	106.0	0.060	1.804	111.0	0.063	0.823	96.4	0.073	2.592	66.0	0.075	1.881	72.4	0.083	1.075	55.1	0.118	2.103	78.3	0.069	2.014	84.0	0.077	0.477	68.4	0.096
135	20	0.566	106.8	0.061	1.686	111.6	0.064	0.518	96.9	0.075	2.407	66.1	0.080	1.851	72.1	0.087	0.891	54.8	0.120	2.236	78.7	0.071	2.032	84.1	0.079	0.553	68.5	0.096
140	34	0.657	107.6	0.062	1.583	112.2	0.065	0.292	97.5	0.077	2.221	66.2	0.084	1.832	71.8	0.090	0.705	54.6	0.121	2.366	79.2	0.073	2.099	84.3	0.080	0.650	68.7	0.097
145	39	0.797	108.7	0.062	1.480	113.1	0.066	0.167	98.1	0.079	2.006	66.3	0.087	1.828	71.7	0.092	0.497	54.4	0.121	2.479	79.7	0.074	2.217	84.5	0.080	0.778	69.0	0.097
150	54	0.973	109.9	0.063	1.367	114.3	0.066	0.186	98.9	0.080	1.743	66.5	0.089	1.836	71.8	0.092	0.279	54.3	0.118	2.591	80.2	0.074	2.404	84.9	0.079	0.955	69.3	0.097
155	51	1.194	111.2	0.062	1.259	115.6	0.066	0.378	100.0	0.079	1.435	66.7	0.087	1.846	72.0	0.090	0.074	54.3	0.114	2.751	80.8	0.073	2.684	85.5	0.077	1.202	69.8	0.095
160	65	1.485	112.4	0.060	1.220	117.0	0.064	0.745	101.1	0.077	1.088	67.0	0.083	1.835	72.4	0.085	−0.091	54.6	0.110	2.967	81.5	0.072	3.042	86.2	0.074	1.514	70.4	0.093
165	53	1.834	113.7	0.058	1.261	118.3	0.060	1.272	102.2	0.073	0.700	67.4	0.078	1.799	73.1	0.077	−0.200	54.9	0.106	3.214	82.3	0.069	3.442	87.0	0.070	1.871	71.2	0.091
170	46	2.210	115.0	0.055	1.332	119.8	0.055	1.903	103.4	0.070	0.285	68.0	0.071	1.739	73.9	0.069	−0.261	55.1	0.147	3.466	83.1	0.066	3.852	88.0	0.064	2.249	72.0	0.089
175	24	2.601	116.4	0.052	1.410	121.2	0.050	2.579	104.6	0.068	-0.136	68.6	0.064	1.671	74.8	0.061	−0.296	55.4	0.099	3.728	84.0	0.064	4.268	88.9	0.059	2.638	72.8	0.087

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night intervals, either arbitrarily or according to a patient diary, allow a quantification of the nocturnal BP fall, or "dipping," both in absolute and relative terms. Alternative methods include the calculation of cumulative sums *(51)*, chronobiological cosinor analysis *(52)*, and Fourier analysis, which is the simultaneous application of several cosine functions *(53)*.

Even though definitions of "non-dipping" vary, the prognostic relevance of the non-dipping phenomenon has been demonstrated in adults with renal failure *(54)* and in the general population *(45)*. Controversy persists about the physiological basis of circadian and ultradian BP rhythms. While evidence from shift workers suggests that BP rhythms are determined largely externally by physical activity, the fact that disturbances of the diurnal BP pattern are found in a variety of pathological conditions has led to the suggestion that an endogenous rhythm of autonomic nervous activity is at least partly responsible for the generation of circadian BP rhythmicity.

Fourier analysis appears to be superior to linear analysis because there is no need to define day and night intervals, which presuppose an activity-related origin of BP variations. The combination of several rhythms allows a more detailed and flexible description of the 24-h period than the original cosinor method.

Circadian cardiovascular rhythmicity is present in the majority of healthy children and adolescents with an attenuation of 24-h heart rate periodicity during puberty. In addition, ultradian rhythms are found in the majority of healthy children, with an age-related shift from 8-h to 6-h or 12-h predominant rhythmicity *(8)*. Pediatric reference ranges of ultradian rhythms have been provided *(8)*. Compared to these reference data children with chronic kidney disease show marked blunting and delay of the rhythmicity of both BP and heart rate *(55)*. Changes in ultradian and circadian rhythms were independent of each other. Also the ultradian BP amplitudes but not the circadian amplitudes or conventional dipping parameters were correlated to indices of renal function, raising the possibility that ultradian rhythms play an independent role in chronic kidney disease. Current evidence suggests that, whereas normal circadian BP variation is a positive predictor of cardiovascular outcome, ultradian BP variability is more associated with disease states. Increased BP variability has been demonstrated in obese children and is most likely related to increased sympathetic nervous system activation in obesity-related hypertension *(56)*. In adults, greater BP variability has been correlated with the development of hypertensive left ventricular hypertrophy *(57)*.

Reproducibility of ABPM

One of the key advantages of ABPM is its superior reproducibility in comparison to casual BP measurements, which has been demonstrated in adults *(58–60)* and children *(61)*. Excellent reproducibility has also been shown for the nocturnal dipping phenomenon *(62)*. Still, a certain degree of BP variability will be found even with ABPM; in children with borderline hypertension, more than one ABPM may be required to judge the consistence of elevated blood pressure *(63)*.

In view of the growing evidence for the superior quality of the information provided by ABPM, the persistent reluctance of many health-care providers, regulatory authorities, and industry researchers in accepting the primary use of this methodology in the diagnostic and therapeutic management of pediatric hypertension appears medically and ethically unjustified.

To date the vast majority of pediatric antihypertensive trials have used office BP readings to define primary study endpoints. In view of the numerous ethical and practical challenges associated with the enrollment of children in randomized, controlled antihypertensive drug

trials, the superior sensitivity of ABPM in detecting treatment-induced BP changes provides a strong argument in favor of using this methodology to define primary endpoints in future clinical trials *(61)*.

Also, in the serial evaluation of blood pressure control in children receiving antihypertensive treatment the superior consistency of ABPM provides valuable qualitative and quantitative information, which is highly likely to improve blood pressure control and long-term cardiovascular outcomes.

In conclusion, with its wide availability, proven technical feasibility across the pediatric age range, availability of high-quality pediatric reference data, and superior sensitivity in diagnosing hypertension and detecting pharmacological treatment effects, ABPM should be considered the method of choice for diagnosis and follow-up in pediatric hypertension.

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11 Epidemiology of Essential Hypertension in Children: The Bogalusa Heart Study

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Contents

INTRODUCTION

Cardiovascular diseases including heart attack and stroke remain the leading causes of death and disability in the United States *(1)*. However, the adult heart diseases begin decades earlier *(2)*. Observations from many well-established epidemiologic studies in adults have implicated risk factors, for example, high blood pressure, hypercholesterolemia, and obesity, along with lifestyles of poor diet, smoking, and sedentary behavior, as related to the development of clinical heart disease *(3–5)*. Unfortunately, hypertension is a major public health problem involving over 30% of the adult African-American population *(6)*. Furthermore, a strong relationship has been demonstrated between cardiovascular risk factors and underlying atherosclerotic, hypertensive vascular abnormalities at autopsy both in adults and in children and adolescents *(3,4)*. The occurrence of anatomic changes at a young age is the most compelling evidence that the adverse effects of risk factors such as hypertension are not limited to adult heart disease but that hypertensive cardiovascular–renal diseases begin in childhood *(7,8)*. Epidemiologic studies at a young age now provide considerable understanding of the early natural history of high blood pressure and

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_11
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the hypertensive disease leading to clinical events. In this chapter we will summarize key findings from the Bogalusa Heart Study and other important works.

PREVALENCE OF HYPERTENSION

The prevalence of hypertension in children is influenced by the definition of what may be considered normal in growing children and methods used to obtain blood pressure levels. Indirect measurement is the accepted form, and proper cuff size is essential for valid measurements *(9–11)*. Because of considerable variation in blood pressure levels measured in childhood, replicate measures of blood pressure in the resting state best reflect an individual's blood pressure level *(11,12)*. However, the precise level defining hypertension in childhood is controversial. Early recommendations listed normal and elevated percentiles of blood pressure by gender and age *(13)*. Current guidelines improved the definition of hypertension in growing children by evaluating blood pressure levels as a function of height *(11)*. The importance of height as a determinant of blood pressure was shown in the Bogalusa Heart Study where 39% of the variability in systolic blood pressure was related to body size and not age *(14)*. Since children mature at different rates, taller children of the same age equate with a distribution at higher levels (Fig. 1). Based on this finding, it is recommended that blood pressure levels be related to height for defining abnormality.

Additional controversy exists around which gender- and height-derived percentiles are abnormally high. Current pediatric BP guidelines define hypertension as persistent BP levels above the 95th percentile for age, gender, and height *(11)*. However, anatomic changes

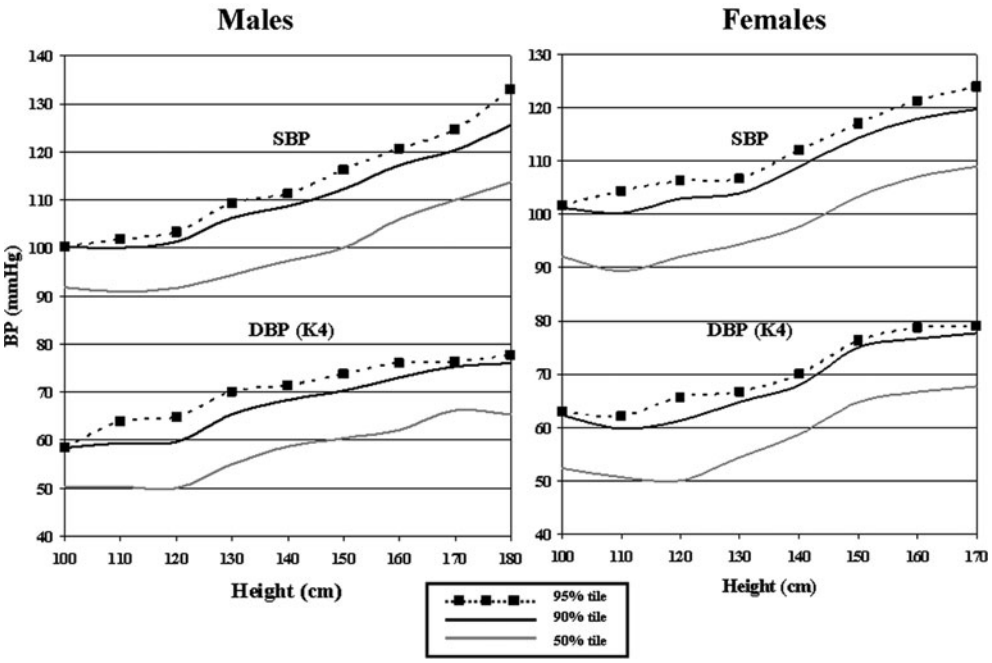

Fig. 1. Percentile levels for blood pressure by height for males and females. *The Bogalusa Heart Study* (*N*= 3352). Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure *(170)*.

in target organs such as development of left ventricular hypertrophy (LVH) are seen to occur at levels just above the 90th percentile *(15)* with increased left ventricular posterior wall measurements seen to occur with BP above the 80th percentile *(16)*. Furthermore, epidemiologic evidence demonstrates that presence of pre-hypertension (levels above the 90th percentile) has a sensitivity of 33.3% in predicting future adult hypertension *(17)*. Data from the National Childhood Blood Pressure database suggests that presence of pre-hypertension may predict progression to sustained hypertension in up to 12–14% of children in only 2 years of follow-up *(18)*. Bogalusa Heart Study data also indicate the importance of identifying youth crossing blood pressure percentiles since a change in blood pressure in youth was independently associated with being classified as prehypertensive or truly hypertensive as an adult *(19)*.

The definition of diastolic hypertension has also varied over time. Some have advocated abandoning diastolic blood pressure measurements in children altogether *(20)*. Others suggest reporting both K4 and K5 *(21),* using K4 up to a certain age and then shifting to K5 *(13)* or using only K4 or K5 diastolic blood pressure measurements *(22,23)*. Although the use of K5 diastolic blood pressure would provide continuity between reporting of childhood and adult values, studies in children have demonstrated a large difference between K4 and K5 levels particularly in young children. One study found 27% of all children aged 5–8 years had at least one of six measurements of K5 near zero, a value with limited physiologically significance *(22)*. Furthermore, K4 diastolic blood pressure measurements are more reproducible in childhood and are a better predictor of adult hypertension (Fig. 2) *(24)*.

Other considerations for choice of childhood blood pressure norms exist. The most recent published guidelines for blood pressures in children base normal values on data averaged from multiple epidemiologic studies *(11)*. However, only a single measurement, often the first and only measurement, is used. The use of a single measurement to define normal blood pressure levels is markedly limited by the observed and significant within-subject variation in blood pressure levels. Replicate and serial measurements, four to six, are needed to obtain levels characteristic of a given individual or misclassification of subjects may occur *(12,25)*. Furthermore, a single blood pressure recording may be subject to the 'first

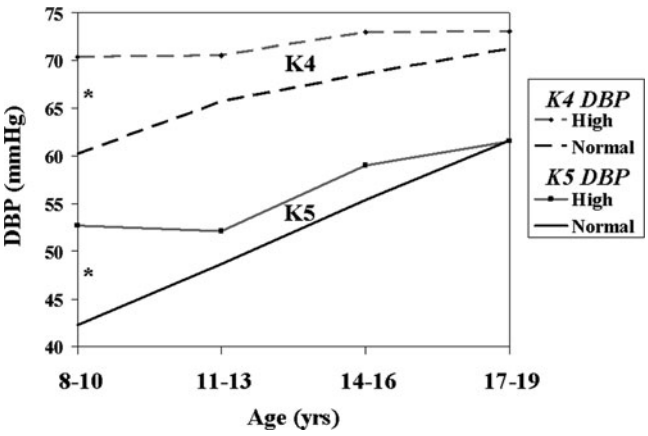

Fig. 2. Childhood K4 and K5 related to normotensive and hypertensive adults, respectively. *The Bogalusa Heart Study* (N=1017, $^*p$ values for difference between levels of DBP measured in childhood for normotensive and hypertensive adults are $\leq$0.05 for ages 8–16) *(24)*.

reading effect' both with automatic Dinamap-type devices *(12,26)* and with a mercury sphygmomanometer; the first reading may be higher than an individual's intrinsic blood pressure *(25)*. 'White coat' hypertension is a real phenomenon; however, it may be overdiagnosed with the use of a single blood pressure recording *(27,28)*. Averaging six readings of BP has led the Bogalusa Heart Study to publish blood pressure norms that are lower than national guidelines *(11)* by 5–10 mmHg for systolic blood pressure (slightly less for diastolic blood pressure) *(29)*. Circadian variation in BP levels also exists. Nighttime levels measured with 24-h ambulatory blood pressure monitoring (ABPM) dip at least 10% lower than daytime values in normal individuals. Although new guidelines are available on recommended use of ABPM in children and adolescents *(30),* widespread use of this technique is limited by lack of availability of normative data across diverse races, genders, and ages *(31)*. Furthermore, at least two repeat 24-h ambulatory recordings are needed to account for 90% of the variability in blood pressure recordings *(32)*. Similarly, African-American children in Bogalusa have been shown to have higher resting blood pressure levels than white children *(33)*. Therefore, insufficient numbers of non-white participants in nationally published averages may make that data less readily applicable to minority populations.

Despite the difficulties in measurement, obtaining blood pressure levels can identify children needing immediate intervention and is helpful in predicting adult hypertension since blood pressure levels 'track' (remain in respective rank) over time. Tracking correlation coefficients for blood pressure range from 0.36 to 0.50 for systolic blood pressure and from 0.29 to 0.42 for diastolic blood pressure over 15 years of follow-up (Fig. 3) *(34,35)*. Children in the highest quintile for blood pressure had a nearly fourfold increase in risk of being diagnosed with clinical hypertension as an adult. Multiple elevations in blood pressure levels recorded as a child improved the ability to predict adult hypertension *(34)*.

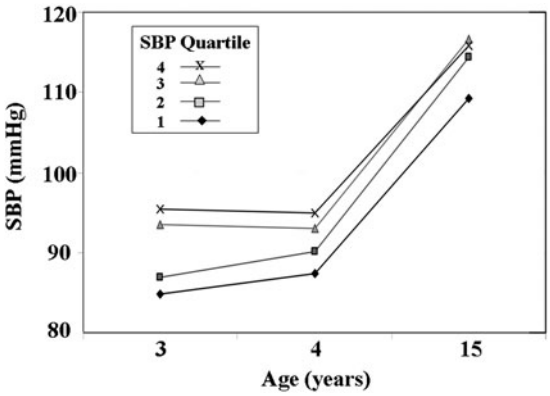

Fig. 3. Tracking of systolic blood pressure (persistence of quartiles) over 15 years of follow-up starting at the age of 2 years. *The Bogalusa Heart Study* (*N*=185) *(35)*.

CHARACTERISTICS OF THE HYPERTENSIVE CHILD

The characteristics of the hypertensive child represent the underlying determinants of hypertension.

Anthropometrics

Although height relates strongly to blood pressure levels in growing children, body fatness influences adult *(36)* and childhood blood pressure levels even after adjustment for height *(37,38)*. This relationship between obesity and blood pressure is stronger in white children than African-American, especially in African-American males *(9)*. Central body fat distribution may be even more important as it significantly relates to systolic blood pressure in children aged 5–17 years even after adjustment for peripheral body fat while the reverse is not true *(39)*. Furthermore, male children and adolescents with total body fat levels ≥25% were found to be 2.8 times more likely to have higher blood pressure levels than lean children. This remained significant even after adjusting for potential confounding factors such as age, race, and truncal fat pattern *(40)*. Data in females were similar. Which measure of adiposity relates most strongly to blood pressure levels is controversial. In one cross-sectional study, BMI for age was more powerful than waist to height ratio in identifying children with high systolic blood pressure *(41)*. With the trend toward increasing prevalence of overweight children well documented *(42–44)* obesity may be the most important, preventable cause of elevated blood pressure in young people, especially whites.

Renal Function and Electrolytes

Perturbations in renal hemodynamics have long been postulated to be an etiology for adult hypertension *(45)*. In children, a positive relation exists between 24-h sodium excretion, 24-h urine sodium to potassium ratio, and blood pressure for African-American adolescents with higher resting blood pressure levels *(46)*. Interestingly, these relationships were not seen in whites. Additional racial contrasts are seen in other renal factors related to blood pressure. African-American children, especially those with higher blood pressures for age, size, and gender, have lower plasma renin activity than white children (Table 1) *(47)*. However, renin activity correlates with blood pressure only in white youth *(48)*. White children were also more likely to demonstrate both high renin activity levels and insulin resistance as measured by post-glucose load 1-h insulin × 1-h glucose levels *(48)*. African-Americans were also found to have less urine potassium excretion and slightly lower creatinine clearance *(47)*. In a longitudinal study, baseline systolic and diastolic blood pressures were independent predictors of follow-up creatinine 7 years later in African-Americans, while the reverse was not true *(49)*. Young African-American adults also demonstrate greater natriuresis with a negative stool and urine sodium balance and a cumulative potassium balance in response to an oral potassium challenge. These results were not found for whites *(50)*. It should be noted that additional studies proved no significant difference among these two races in overall sodium to potassium dietary intake *(51)*. Unfortunately, two-thirds of these school-age children had sodium intakes above the recommended 2 g/day and 50–70% had potassium intakes below the recommended daily allowance (2 mEq/kg/day) *(52)*. It is clear that dietary modification may be an important step in preventing hypertension in genetically salt-sensitive individuals, especially in African-Americans.

Neural Mechanisms

While the hypertension in African-American adolescents from the above observations seems to be driven by renal mechanisms, elevated blood pressure in whites may have neural, specifically, sympathomimetic origins. White children demonstrate higher dopamine-β-hydroxylase levels regardless of resting blood pressure levels (Table 1) *(46)*.

Table 1
Plasma Renin Activity, Urine Potassium Excretion, and Serum Dopamine-β-Hydroxylase Levels by Blood Pressure Stratum in Children: The Bogalusa Heart Study *(47)* (N=272)

	Race	*Gender*	*1 (Low BP)*	*2*	*3*	*4*	*5 (High BP)*
Plasma renin activity (ng/mL/min)	White	Male	5.7 (±1.7)	7.1 (±1.7)	6.6 (±1.9)	7.6 (±2.1)	8.6 (±2.4)
		Female	7.4 (+1.1)	6.5 (+1.3)	5.9 (+1.6)	7.7 (+2.3)	8.0 (+2.4)
	African-American	Male	6.1 (±3.1)	6.9 (±2.2)	4.2 (±1.1)	4.1 (±1.3)	3.7 (±2.5)
		Female	3.5 (±2.0)	6.2 (±1.9)	5.0 (±1.2)	7.0 (±2.1)	4.5 (±1.1)
24-h urine potassium excretion (mEq/24-h)	White	No gender differences found	33.2 (±4.9)	42.0 (±5.6)	34.2 (±7.2)	44.7 (±10.2)	38.8 (±6.8)
	African-American		24.8 (± 5.7)	26.5 (±4.2)	27.4 (±4.4)	29.4 (±5.0)	29.8 (±11.6)
Serum dopamine-β-hydroxylase (mmol/min/L)	White	Male	37 (±6)	29 (±7)	32 (±8)	28 (±7)	33 (±8)
		Female	30 (±12)	25 (±8)	27 (±8)	29 (±7)	35 (±6)
	African-American	Male	26 (± 13)	23 (±5)	17 (±5)	24 (±6)	23 (±13)
		Female	17 (±7)	20 (±7)	22 (±5)	22 (±6)	19 (±18)

This suggests sympathetic predominance exits in white children *(47)*. The faster heart rates seen at higher levels of blood pressure in white children, especially boys, support this theory *(46)*. Other supportive data are found in studies of heart rate variability in adults where sympathetic predominance at rest is found as compared to age-matched controls, with the degree of abnormality correlating with severity of hypertension *(53)*. Adult hypertensives also demonstrate loss of the circadian rhythm of the low-frequency component measured by heart rate variability *(54)*. In a study using heart rate variability in children, healthy white male adolescents regardless of blood pressure level demonstrated higher sympathetic tone and lower parasympathetic tone than African-Americans. A trend for sympathetic predominance in the higher blood pressure group was noted for both races *(55)*. Again, it was hypothesized that variations in sympathetic nervous system function occur among the races in regard to initiation of essential hypertension. Studies of systolic blood pressure and heart rate show a higher 'double product' in white children also indicative of greater sympathetic tone *(56)*. However, there may be a crossover to higher sympathetic levels in African-Americans around 25 years of age accounting for the higher blood pressure and heart rate found in adults of African descent as compared to subjects of white Americans *(57)*.

Stress Responses

Not only do racial differences exist in resting autonomic tone but there are also differences demonstrated in response to stress for both children *(58)* and adults *(59)*. African-American children performing cardiovascular response tests have higher maximal stressed systolic blood pressure than whites regardless of resting blood pressure levels (Fig. 4) *(60,61)*. For the African-American adolescents with elevation of resting blood pressure, the systolic levels of blood pressure especially during orthostatic and cold pressor testing exceeded those of the other race–sex groups *(47,61)*. Peripheral vasoconstriction is also much more pronounced in African-American children in response to alpha-adrenergic stimulation such as produced by cold stress *(62,63),* a finding that has been noted in normotensive African-American adults *(64)*. In addition, mental stress in hypertensive African-Americans results in diminished cardiac sympathomimetic tone with higher peripheral

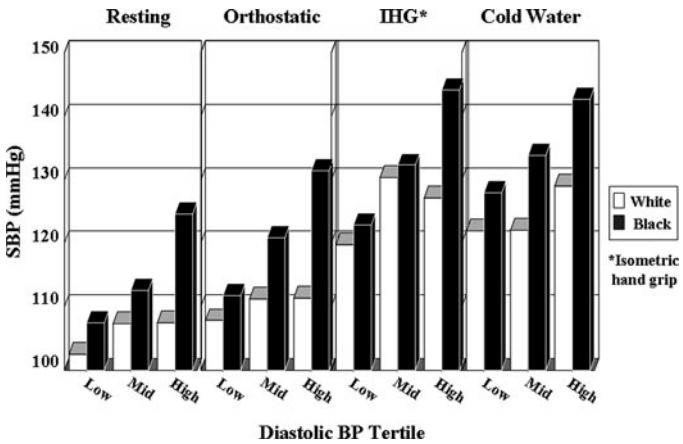

Fig. 4. Resting and maximal stress SBP levels in boys aged 7–15 years by race and resting diastolic blood pressure tertile. *The Bogalusa Heart Study* (N=136, p values for all race difference in maximal stressed SBP are ≤ 0.01) *(61)*.

vascular response *(65)*. In contrast, white males with borderline high blood pressures have a greater increase in cardiac index in response to stress *(63)* while African-American subjects exhibit increases in vascular tone *(66–68)*. Sympathetic predominance in white children has also been shown by heart rate variability data collected during reactivity testing with a trend toward sympathetic predominance in hypertensives of both races *(69)*. These data show racial differences occur in response to stress even in early borderline hypertension. There may be underlying African-American/white differences in autonomic tone or response of the nervous system to stress with different types of adrenergic receptors stimulated to different degrees. Blood pressure responses to stress may also be a marker for the individual genetically predisposed toward adult hypertension. Parker et al. found that peak blood pressure in children during orthostatic stress, isometric handgrip, and cold pressor testing helped predict future blood pressure even after adjusting for baseline blood pressure levels *(67)*. Furthermore, blood pressure reactivity has been found to be predictive of future left ventricular mass corrected for body size especially in African-Americans *(70)*. Interestingly, both blood pressure response to exercise and left ventricular mass have also been found to predict future blood pressure *(71)*. Left ventricular mass likely represents the sum of long-term effects of blood pressure both at rest and during stress *(71)*. A combination of resting and peak exercise blood pressure levels along with measurement of left ventricular mass may prove to be better predictors of adult hypertension.

Hyperdynamic Circulation

African-American/white contrasts have been demonstrated in resting measures of cardiovascular function. White children have been found to have higher resting heart rates *(61)* and higher cardiac output as measured by echocardiography (Fig. 5), and blood pressure levels were positively correlated with resting cardiac output and stroke volume *(68)*. In contrast, African-American children were found to have higher peripheral vascular resistance *(68)*. These findings in children are notable since studies in adults have suggested that a hyperdynamic state with increased cardiac output due to enhanced contractility occurs early in persons genetically susceptible to hypertension *(72)*. Later, cardiac output may

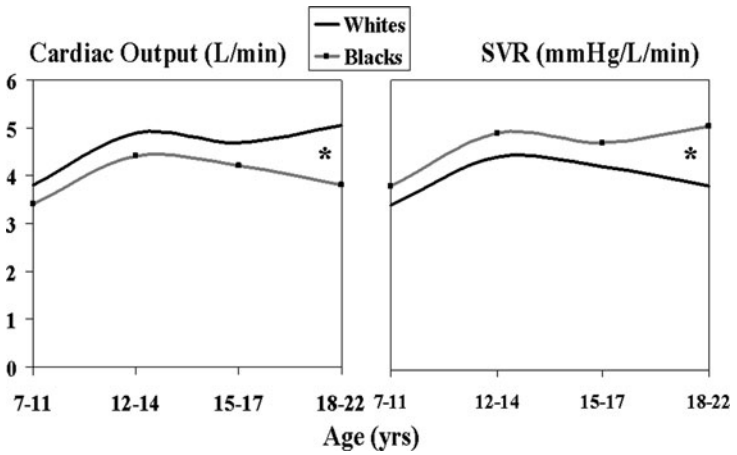

Fig. 5. Cardiac output and systemic vascular resistance (SVR) measured by echocardiography in males by race and age. *The Bogalusa Heart Study* (N=651, $^*p$ for race difference $\leq$0.01) *(68)*.

become normalized due to a sustained increase in peripheral vascular resistance occurring with a progressive downregulation of beta-receptors. This may eventually result in clinical hypertension *(63)*.

Obesity, well known to increase the risk of hypertension, may also increase risk for development of a hyperdynamic circulatory pattern. The 'double product,' or heart rate × blood pressure, has been described as a measure of hyperdynamic circulation *(56)*. Boys with obesity were found to have a higher 'double product' suggesting a link between weight and chronic cardiac stress through an effect on myocardial oxygen consumption *(56)*. Investigators have also found that obese boys (percent body fat >75th percentile) with hyperdynamic circulation (high pulse pressure and heart rate) have higher systolic blood pressure, triglyceride, VLDL cholesterol, and fasting insulin levels regardless of age and race (Fig. 6) *(73)*. These features of adult-type syndrome X persisted when the subjects were followed over 3 years ('tracking') *(73)*. These data suggest that an obesity-insulin-induced hyperdynamic circulation may be an early feature of type 2 diabetes and occurs even at young ages. The much greater frequency of pre-diabetes and metabolic syndrome reported in our nation in recent years *(74)* may impact the incidence of hypertension if obesity control measures are not promptly enacted *(75)*.

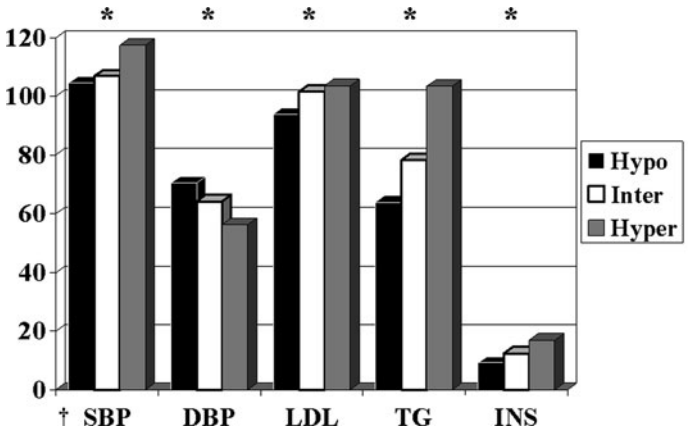

Fig. 6. Effect of hyperdynamic circulation on blood pressure, lipids, and insulin in obese boys (body fat >75%) aged 8–17 years. *The Bogalusa Heart Study* (*N*=96). (*N*=2229, *p* values for slope of linear regression of variables on hemodynamic status after adjusting for age and race are all ≤0.003). †Units are as follows: SBP and DBP, mmHg; LDL-C, HDL-C, and TG, mg/dL; insulin, μU/mL *(73)*.

Effect of Insulin on Hemodynamics

Glucose loading experiments in children have been performed to further investigate the relationships between carbohydrate metabolism and cardiovascular function. White children had higher 1-h plasma glucose levels than African-Americans, and fasting glucose levels in whites were seen to increase with each successively higher quintile of resting blood pressure (Fig. 7) *(47)*. A trend for increasing fasting insulin levels with higher levels of blood pressure was also seen in white boys even after adjusting for body weight *(47)*. When the 'peripheral insulin resistance' product was calculated for white boys (1-h glucose in mg/dL multiplied by the 1-h insulin level in μU/mL), there was a significant increase at higher levels of blood pressure. White subjects with a higher insulin resistance product demonstrated a positive relationship between fasting glucose and resting blood pressure

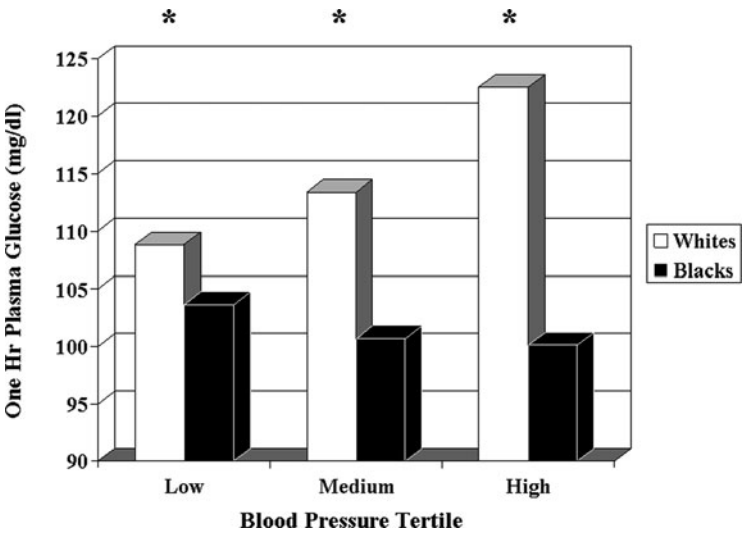

Fig. 7. One-hour plasma glucose levels by race and blood pressure level in children aged 7–15 years. *The Bogalusa Heart Study*. (N=270, $^*p \leq 0.05$ for the slope of the linear regression of 1-h glucose on blood pressure stratum in white subjects) *(47)*.

adjusted for body size *(76)*. Further study has confirmed racial differences in carbohydrate metabolism with African-American children demonstrating significantly higher insulin and lower glucose levels than whites *(77)*. Both race and ethnicities demonstrated a positive relationship between metabolic measures such as insulin and glucose and blood pressure levels in cross-sectional studies *(78)*; however, longitudinal analyses found that the correlation remained significant with follow-up blood pressure only in whites *(79)*. Multivariate models showed a significant relationship between fasting insulin and both systolic and diastolic blood pressure in children (5–12 years) and young adults (18–26 years) independent of glucose level and body fatness (Table 2) *(78)*. Weaker relationships were found during puberty (13–17 years) which may have been due to the complex and variable rates of change of sex hormones and growth velocity during these ages *(78)*. The stronger relationship between insulin and systolic rather than diastolic blood pressure has been postulated to be due to the effect of insulin on pulse pressure *(80)*. These studies suggest that the relationship between insulin and blood pressure may differ between individuals of different genetic/racial makeup resulting in variable alterations in sympathetic tone, sodium reabsorption by the distal renal tubules, or amount of vascular hypertrophy leading to distinct etiologies for the same manifestation (hypertension) *(78,81)*.

Regardless of ethnicity, levels of fasting insulin demonstrate tracking (persistence of relative rank over time with r=0.23–0.36) *(82)*. This is significant because subjects in the highest quartile of insulin at baseline demonstrated higher levels of systolic blood pressure (+7 mmHg), diastolic blood pressure (+3 mmHg), body mass index (+9 kg/m^2), triglycerides (+58 mg/dL), LDL cholesterol (+11 mg/dL), VLDL cholesterol (+8 mg/dL), and glucose (+9 mg/dL) with lower levels of HDL cholesterol (–4 mg/dL). They were 3.3 times more likely to report a parental history of diabetes and 1.2 times more likely to report a family history of hypertension *(82)*. In subjects with tracking of elevated insulin levels, the prevalence of adult hypertension was increased 2.5-fold with increased rates for obesity (3.6-fold) and dyslipidemia (3-fold) also reported *(82)*. These data introduce the concept of 'clustering' of cardiovascular risk factors where elevated levels of multiple risk factors are

Table 2
Independent Variables Associated with Blood Pressure by Age[a]: The Bogalusa Heart Study *(78)*

5–8 years (N=717)	*9–12 years (N=939)*	*13–17 years (N=1048)*	*18–26 years (N=814)*
		Systolic blood pressure	
BMI	BMI	Age	Gender
Subscapular skinfold	Insulin	Gender	BMI
Insulin	Glucose	BMI	Insulin
Glucose		Race	Race
		Glucose	
$R^2 = 0.27$	$R^2 = 0.25$	$R^2 = 0.13$	$R^2 = 0.16$
		Diastolic blood pressure	
BMI	Subscapular skinfold	Gender	BMI
Age	Insulin	Age	Gender
Subscapular skinfold	Glucose	Glucose	Age
Race	Gender		Insulin
	BMI		
$R^2 = 0.13$	$R^2 = 0.16$	$R^2 = 0.10$	$R^2 = 0.06$

[a]Listed in order of acceptance by the stepwise regression model. BMI indicates body mass index. All $p \leq 0.05$.

found to exist together in many adults leading to a multiplicative risk of cardiovascular diseases. Clustering has also been demonstrated in children with persistently higher levels of blood pressure contributing most strongly to the prediction of multiple risk factor clustering as an adult *(83)*. However, the adult metabolic syndrome with insulin resistance is likely the result of the eventual congruence of different physiologic processes occurring in childhood. Factor analyses of Bogalusa Heart Study data found that both metabolic (insulin resistance, dyslipidemia, obesity) and hemodynamic (insulin resistance, blood pressure) clustering in childhood may be operating as precursors of adult metabolic syndrome *(84)*. Further analyses suggest that these clustering patterns differ by race/ethnicity. Although multivariate analyses revealed that metabolic syndrome resulted from three different factors, they differed by race. In whites, the clusters were blood pressure and adiposity; lipids and adiposity; and insulin resistance, renin levels, and adiposity. For African-American subjects, renin did not contribute *(85)*. The importance of each of the factors (magnitude of the path analysis coefficients) in explaining metabolic syndrome was greater for whites except for the effect of age on mean arterial pressure which was stronger in blacks *(85)*. Regardless of the pathway taken by individuals of differing genetic or race and ethnic backgrounds, it is clear that the pathophysiologic changes leading to metabolic syndrome in adults begin in childhood.

Uric Acid

Animal studies suggest a role for uric acid in the pathogenesis of hypertension *(86)*. This may be through modulation of oxidative stress resulting in stimulation of the renin–angiotensin system or by stimulation of vascular smooth muscle proliferation *(87)*.

Therefore, it is not surprising that a relationship was found between childhood uric acid levels and change in uric acid levels and eventual adult blood pressure *(88)*. This relationship persisted even after adjusting for traditional cardiovascular risk factors *(89)*.

Family History

Predicting and preventing adult heart and kidney diseases are the major motivations for examining children with potential hypertension. Family history is an important component of these evaluations as parental history provides a surrogate measure of future cardiovascular disease. In a study of 3,312 children aged 5–17 years, significant correlations were found between levels of risk factors in children and family history even after adjusting for age, race, and gender *(90)*. However, independent associations between childhood risk factor levels and family history were only found for combinations of parental diseases such as heart attack in the father plus high blood pressure or diabetes *(90)*. In contrast, when childhood blood pressure rank was analyzed longitudinally over 9 years, family history of hypertension alone was found to be an independent predictor of future systolic blood pressure in these children *(91)*. Similar relationships between childhood blood pressure levels and parental history of hypertension were found in the Muscatine Study *(92)*. When younger children were studied (birth to 7 years of age), the strongest relationships were found between parental and child height and weight *(93)*. However, when the parents' systolic blood pressures were related to their childrens' levels with regression coefficients, significant relationships were found which tended to increase with the child's age *(93)*. It seems logical that as parents age, they begin to develop morbidity from elevated levels of risk factors that were not apparent earlier. In fact, in a study of 8,276 subjects, the prevalence of parental cardiovascular disease was greater in subjects aged 25–31 as compared to the 5- to 10-year-old group *(94)*. This included an increase in reporting of positive family history of hypertension by up to 32% depending on race *(94)*. Furthermore, children of hypertensive parents had higher blood pressure after 10 years of age regardless of weight and also demonstrated increased prevalence of dyslipidemias *(94)*. Racial differences were also seen with white children, especially boys, demonstrating higher LDL cholesterol levels and reporting parental history of heart attack while African-Americans had higher insulin levels and were more likely to report parental hypertension *(94)*. Ambulatory blood pressure studies have also demonstrated the importance of family history of hypertension *(32)*. When ambulatory blood pressure load was calculated, the percentage of readings above the race-, gender-, and height-specific 90th percentile for systolic and diastolic blood pressure was found to be greatest in children with high resting blood pressure and a family history of hypertension. However, children with low resting blood pressure and a positive family history of hypertension also had higher ambulatory blood pressure load than normotensive children without a family history (Fig. 8) *(32)*.

Genetic Influences

Advances in genetic testing techniques have opened new avenues for evaluating the genes associated with regulation of blood pressure levels. Estimation of the heritability of longitudinal blood pressure levels (total area under the curve) was 0.66 for systolic and 0.68 for diastolic blood pressure in a sub-study using 775 white siblings *(95)*. When 357 highly polymorphic microsatellite markers were typed, linkage analyses found genes on chromosomes 2 and 18 for diastolic blood pressure and chromosome 4 for both systolic and diastolic blood pressure to be important (Fig. 9) *(95)*. Several hypertension candidate

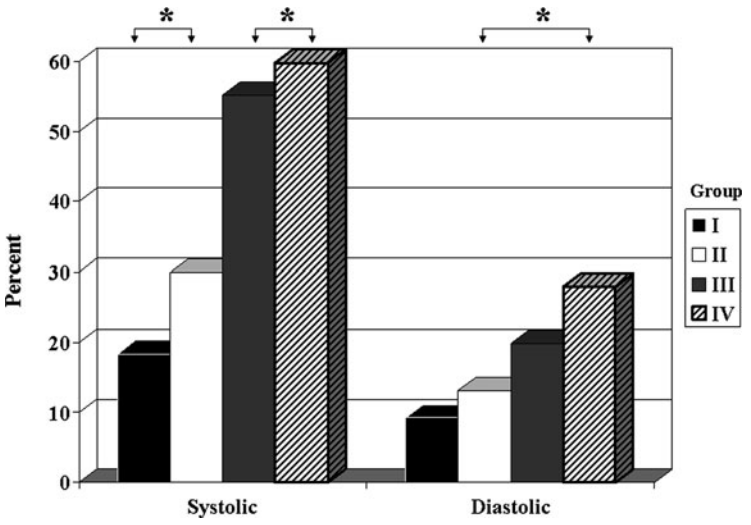

Fig. 8. Frequency of ambulatory blood pressure readings greater than the 90th percentile by blood pressure and parental history group in children aged 12–21 years. *The Bogalusa Heart Study* (*N*=57; **p* for difference between groups indicated by arrows ≤0.01). I = low blood pressure group, no parental hypertension; II = low blood pressure group, +parental hypertension; III = high blood pressure group, no parental hypertension; IV = high blood pressure group, +parental hypertension *(32)*.

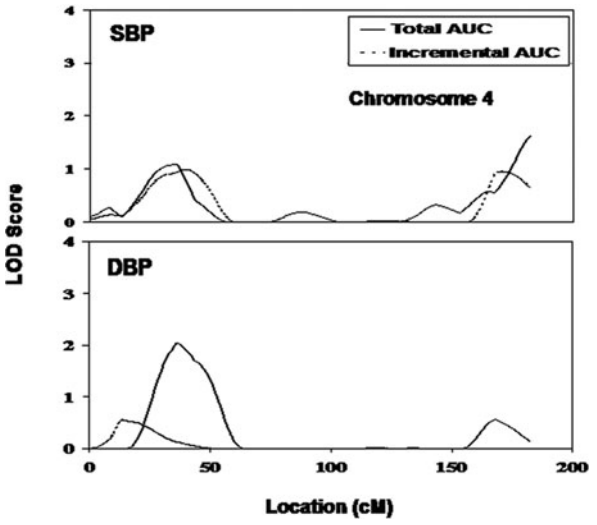

Fig. 9. Multipoint linkage results for total and incremental AUC for blood pressure in white siblings on chromosome 4. *The Bogalusa Heart Study*. LOD score peak = 2.0 for DBP at 36 cM near the marker D4S2994 (2-point LOD = 2.1) with weak linkage to SBP (total AUC LOD = 1.1 at 35 cM; SBP incremental AUC LOD = 0.99 at 39 cM). Also, SBP had total AUC LOD = 1.6 at 182 cM and incremental AUC LOD = 0.95 at 170 cM near the q-terminal of chromosome 4 2. AUC=area under the curve (mmHg) divided by the number of follow-up years. Total AUC was adjusted for age, sex, and body mass index; incremental AUC was adjusted for age, sex, body mass index, and baseline blood pressure *(95)*.

genes are located in these areas such as alpha-adducin, beta-adducin, sodium bicarbonate co-transporter, and G protein-coupled receptor kinase 4 *(95)*. Other candidate genes have also been evaluated. The non-carriers of the 894T (vs G) polymorphism of the endothelial nitric oxide synthase gene had significantly higher blood pressure especially if they were also insulin resistant *(96)*. Non-carriers of the T allele also were more likely to have a greater long-term burden of blood pressure (area under the curve) since childhood but this was only true for females *(97)*.

Birth Weight

Retrospective studies of adults have found an association between adult hypertension and low birth weight *(98,99)*. The 'fetal origins' hypothesis suggests that fetal programming by under nutrition in utero may initiate processes such as reduced numbers of nephrons in the kidney or changes in other organs, resulting in chronic diseases later in life like hypertension *(100)*. Postnatal influences, such as the increased metabolic demands imposed by the development of obesity, may amplify the effects of fetal programming *(101)*. However, data from epidemiologic studies show inconsistent relationships between birth weight and adult blood pressure levels *(102,103)*. Racial and genetic background may be influencing these results as Bogalusa Heart Study data show a stronger relationship between low birth weight and future blood pressure in whites than in African-Americans (Fig. 10) *(104)*. In fact, birth weight may be one factor accounting for race/ethnic differences in adolescent blood pressure levels *(35)*. Also, birth weight may be a better predictor of blood pressure levels when subjects are young adults *(105)* rather than during childhood *(103)* and may be better at predicting longitudinal blood pressure trends *(106)* as there has been more time to display a mature blood pressure phenotype. Additional prospective studies such as the National Children's Study (www.nationalchildrensstudy.gov) co-sponsored by the National Institute of Child Health and Human Development, the National Institute of Environmental Health Sciences, the Centers for Disease Control and Prevention, and the US Environmental Protection Agency are in progress. These studies may shed more light on this issue by factoring in influences such as gestational age *(107)*; disproportionate, head-sparing low birth weight *(98)*; and maternal factors *(108)*.

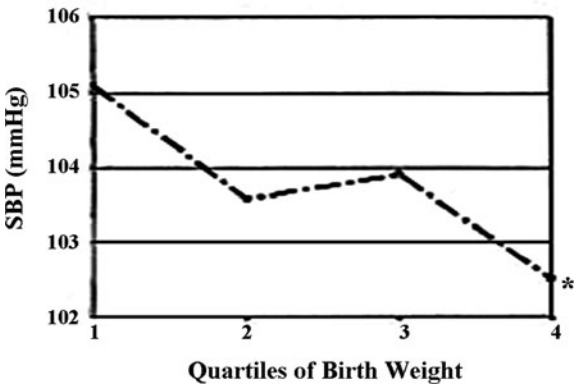

Fig. 10. Mean systolic blood pressure by quartiles of birth weight, adjusted for age, sex, ethnic group, and BMI. *The Bogalusa Heart Study* (N=1155, $^*p \leq 0.01$ for linear trend across quartiles of birth weight) *(104)*.

SUBCLINICAL TARGET ORGAN DAMAGE, 'SILENT DISEASE'

Subclinical target organ damage occurs in children with higher levels of blood pressure and can be measured by invasive and non-invasive techniques.

Autopsy Studies

Beginning in 1978, autopsies were performed on participants in the Bogalusa Heart Study in Louisiana who died between the ages of 3 and 31 years *(2,4,109)*. Most deaths resulted from vehicular accidents, homicides, or suicides, with only 10% related to natural causes. Tissue samples collected from 85 autopsies included coronary arteries, aorta, kidney, adrenals, and blood. Aortas and coronary arteries were stained with Sudan IV and gross evaluation of fatty streaks and fibrous lesions performed according to protocols developed in the International Atherosclerosis Project *(110)*. Histological evaluations were also performed with anatomic results compared to antemortem cardiovascular risk factor data.

A consistent pattern of associations between lesions and risk factors emerged. Antemortem levels of total and LDL cholesterol were strongly related to extent of fatty streak lesion in the aorta *(2,109)*. Fatty streaks in the aorta and coronary arteries were also related to systolic blood pressure; however, after adjustment for age, the relationship was only found to be significant for the coronaries *(4)*. Importantly, fibrous plaques in coronary arteries, the type of lesions felt to be prone to progression, were also correlated with age-adjusted antemortem systolic and diastolic blood pressure levels (Fig. 11) *(4,109)*. This finding of increased prevalence of fibrous plaques in the coronary arteries of men with hypertension and other cardiovascular risk factors has been confirmed in the Pathologic Determinants of Atherosclerosis in Youth study *(3)*.

Once again race and gender differences were found. Males, especially African-Americans, demonstrated larger areas of the aorta staining for fatty streaks *(111)*. Males, in general, had more progression-prone fibrous lesions in both the aorta and the coronary arteries than females. However, this was especially true for white males *(111)*. Male subjects also demonstrated the strongest relationship between antemortem cholesterol levels and aorta fat streaks with white males showing the greatest correlation between systolic

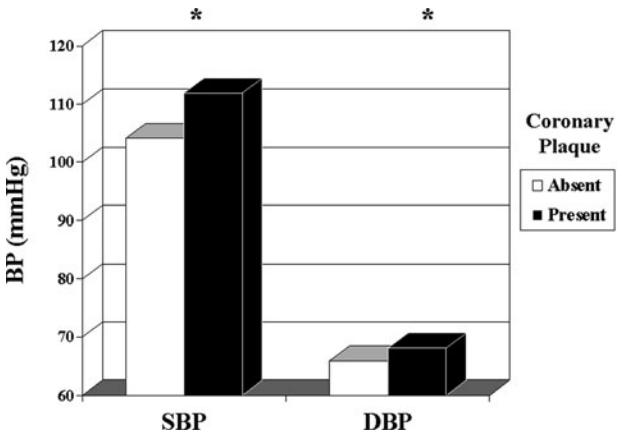

Fig. 11. Levels of blood pressure adjusted for age with and without coronary artery fibrous plaques. *The Bogalusa Heart Study* (N=54, $^*p$ level for blood pressure difference is ≤ 0.04) *(170)*.

and diastolic blood pressure and coronary artery lesions *(111)*. In both genders, histology demonstrated greater aortic foam cell infiltration and further extent and intensity of lipid staining in subjects with higher age-adjusted blood pressure *(4)*. However, only in males, especially African-American males, were a significant correlation found between blood pressure levels and foam cell infiltration and lipid staining in the coronary arteries *(4)*. When intimal thickening of the coronary arteries was studied, a weak relationship was found with antemortem blood pressure levels. However, this coronary artery thickening did relate strongly to hyalinization of renal arterioles *(4)*.

Additional studies have been performed exploring the relationship between blood pressure and renal microvascular abnormalities. A mathematical model was developed to relate quantity of lesions found in renal arteries measuring 50–400 μm and mean blood pressure *(112)*. A linear relationship, mean BP = 1.60 × microvascular lesions +79.7, with correlation coefficient 0.698, was found for all ages *(112)*. The sample studied was from a population with a mean age of less than 20 years. These data strongly confirm that the atherosclerotic-hypertensive process begins in youth, and the degree of vascular involvement correlates with antemortem levels of cardiovascular risk factors including blood pressure levels. Furthermore, the thickening of small renal arteries is consistent with the concept of remodeling outlined by Glagov et al. *(113)* and the observations of vascular changes described by Folkow et al. *(114)* and reviewed by Mulvany *(115)*.

Cardiac Structure and Function

Even before echocardiography was in wide usage, investigators demonstrated that subtle ECG changes possibly representing early left ventricular hypertrophy were apparent in children with higher levels of blood pressure *(116)*. Later epidemiology studies measuring left ventricular thickness by M-mode analyses confirmed this hypothesis by showing a positive correlation between left ventricular wall thickness and systolic blood pressure, even after adjusting blood pressure for body size *(16)*. Other epidemiologic studies in children relating blood pressure levels to left ventricular mass, especially in males, have confirmed these relationships *(15,117–119)*. Longitudinal analyses using Bogalusa Heart Study data have also demonstrated that the cumulative burden of systolic blood pressure from childhood to adulthood is independently associated with indexed left ventricular mass in young adults *(120)*. Childhood diastolic blood pressure is also independently related to concentric left ventricular hypertrophy *(121),* the pattern of left ventricular geometry most strongly linked to adverse cardiovascular outcomes in adults *(122)*. Although resting clinic blood pressure is clearly important, ambulatory recordings may be even more powerful than resting clinic levels in identifying youth at risk for hypertension-related left ventricular hypertrophy *(30)*. This is because there is a strong correlation between ambulatory blood pressure load *(32),* the percentage of blood pressure recordings higher than the 95th percentile, and left ventricular mass index *(123)*. The importance of accurate characterization of blood pressure levels in children for prevention is evident in the observation of thicker left ventricular wall at levels only greater than the 80th percentile *(16)*.

Other cardiovascular risk factors may also increase the risk for development of LVH. In longitudinal studies, linear growth (i.e., height) emerged as the major determinant of heart growth in children *(124)*. Earlier, Voors et al. *(125)* stressed body mass as the major determinant of blood pressure in young children, height related in a linear fashion and weight logarithmically. However, development of obesity was shown to lead to increased left ventricular mass in children and in females with this increased mass, possibly preceding the

development of high blood pressure *(124)*. Obesity in childhood was the only consistent predictor of LVM in adulthood *(120)*. Additionally, left ventricular mass was shown to demonstrate tracking through late childhood and adolescence thus confirming the importance of measuring heart size in children with blood pressure levels at the higher end of the distribution *(124)*. Exploration was also made of the relationships between obesity, metabolic syndrome, and left ventricular mass. Although no direct, independent effect of insulin on left ventricular mass was found in healthy adolescents and young adults of normal weight, in obese persons as measured by increasing subscapular skinfold thickness, increasing fasting insulin level was associated with greater heart mass (Fig. 12) *(126)*. These data suggest that the metabolic syndrome phenotype is likely to relate to target organ damage even in adolescents prior to the development of clinical type 2 diabetes. Genetic influences on left ventricular mass have also been explored. The angiotensinogen gene has been implicated in the initiation of left ventricular hypertrophy. Increasing dosage of the A(-6) allele in the gene in white and African-American subjects was associated with left ventricular mass index despite the great difference in prevalence of the allele between race/ethnicities (in whites 66.6% were carriers while in African-Americans 97% displayed the allele) *(127)*.

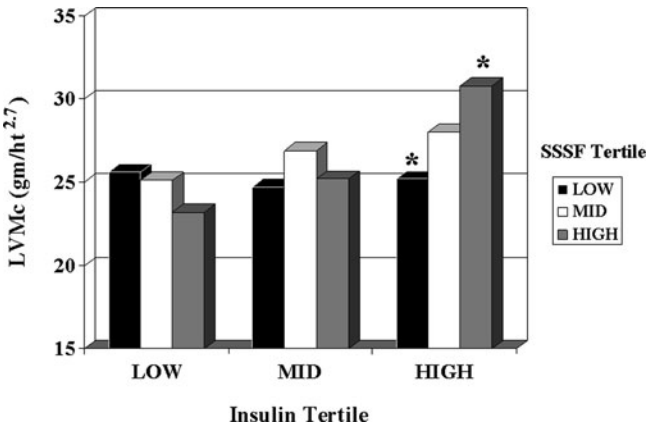

Fig. 12. Left ventricular mass by insulin and subscapular skinfold thickness in children aged 13–17 years. *The Bogalusa Heart Study* (N=216, $^{*}p \leq 0.05$ low SSSF vs high SSSF and mid-SSSF vs high SSSF. SSSF = subscapular skinfold thickness) *(126)*.

The effect of blood pressure level on cardiac function has also been examined. In a sample of children taken from across the entire blood pressure distribution, left ventricular stroke volume and cardiac output were found to be positively correlated with systolic and diastolic blood pressure while ejection fraction and peripheral vascular resistance related significantly to diastolic blood pressure levels *(68)*. With increasing systolic blood pressure and age, an increase in left ventricular output and stroke volume was seen regardless of race or gender. However, further analyses did demonstrate race–gender differences. White males as compared to African-Americans demonstrated greater cardiac output and stroke volume after adjustment for systolic blood pressure and measures of body size (1.25 L/min for ages 18–22 years and 10 mL greater). Conversely, African-American males had higher peripheral resistance (4.5 mmHg/L/min) than whites *(68)*. These findings of increased stroke volume and cardiac output and decreased peripheral vascular resistance in whites as compared to African-Americans were confirmed in a study of over 200

children in Cincinnati, Ohio *(128)*. Autonomic tone may be one factor underlying the racial difference seen in the hemodynamic mechanisms operating in the early phase of hypertension *(68)*. African-Americans demonstrate augmented muscle sympathetic nerve activity (MSNA) associated with higher blood pressures suggesting enhanced alpha-adrenergic sensitivity *(64)*. In contrast, the natural history of hypertension in whites may involve an initial increase in cardiac output followed by downregulation of beta-adrenergic receptors leading to the transition to a progressive increase in systemic vascular resistance *(129)*. Although systolic dysfunction is uncommon in youth, obesity in childhood and hypertension as a young adult were also found to be important predictors of left ventricular dilation in otherwise healthy individuals *(130)*. This suggests that early cardiac decompensation related to cardiovascular risk factors can be identified well before progression to overt left ventricular dysfunction and congestive heart failure. These observations show the importance of obesity in childhood and the burden on the CV system of higher levels of blood pressure even though not at levels considered abnormal by task force criteria.

Vascular Abnormalities

One of the earliest studies of the effect of cardiovascular risk factors on the arterial tree was conducted in the early 1980s *(131)*. In this study, ultrasounds of the carotid artery were performed to measure maximal and minimal diameters during the cardiac cycle. From these data the pressure–strain elastic modulus (E_p), a measure of stiffness that is the inverse of distensibility, was calculated. The study subjects were divided into a low- and high-risk groups based on race, gender, and age-specific tertiles for total serum cholesterol and systolic blood pressure. The high-risk group of children had stiffer carotid arteries with a mean E_p 5.1 kPa higher than in the low-risk group even after controlling for race, sex, and age *(131)*. Subjects with a positive family history for hypertension or diabetes tended to have higher E_p values than those without such a history and those with a history of parental myocardial infarction had a statistically significant increase in carotid artery stiffness *(131)*. Therefore, functional changes in great vessels can be detected in asymptomatic children and adolescents at risk for the development of adult heart disease. The importance of traditional cardiovascular risk factors in determining arterial stiffness was demonstrated in a later study using M-mode ultrasound of the common carotid artery. Systolic and diastolic blood pressure correlated with both Peterson's and Young's elastic modulus, and systolic blood pressure was an independent determinant of both stiffness measures in multivariate analyses *(132)*. Both measures increased, indicating stiffer vessels, with greater numbers of cardiovascular risk factors indicating the important effect of clustering of risk factors on arterial stiffness *(132)*. Further study revealed that candidate genes usually associated with blood pressure regulation exerted influence on carotid stiffness. In African-Americans, the presence of the T allele of the endothelial nitric oxide gene (G894T polymorphism) was associated with lower systolic blood pressure along with significantly lower carotid stiffness (Peterson and Young's elastic modulus) even after adjusting for mean arterial pressure *(133)*.

Studies of the vascular function of other portions of the vascular tree have also been conducted. Distensibility of the brachial artery was measured on 920 healthy young adults who had been followed from childhood as part of the Bogalusa Heart Study. As expected, distensibility tended to decrease with age reaching significance in females *(134)*. However, race and gender differences existed (whites > African-Americans; females > males) even after adjustment for age. When distensibility was plotted as a function of pulse pressure to control for distending pressure, subjects with higher systolic, diastolic, and mean

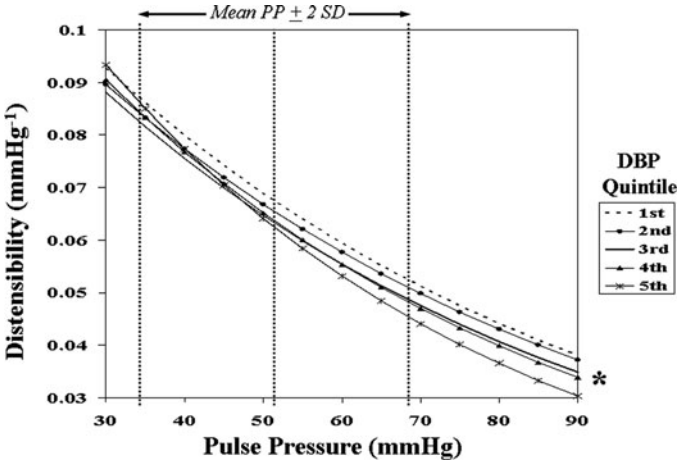

Fig. 13. Brachial artery distensibility as a function of pulse pressure by quintiles of DBP. *The Bogalusa Heart Study* (N=920, $^*p$ for distensibility decrease for the fifth as compared to the first and second quintiles ($p \leq 0.03$)) *(134)*.

arterial pressure had lower distensibility of the brachial artery (Fig. 13). The independent effect of measures of blood pressure on distensibility was confirmed in multivariate analyses *(134)*. Clustering of metabolic syndrome risk factors was also shown to predict diminished brachial artery distensibility *(135)*. Further, pediatric studies suggest that obesity and insulin resistance contribute to deterioration in brachial artery distensibility as early as the adolescent years *(136)*. Longitudinal analyses are needed to explore the effects of childhood levels of risk factors on adult measures of non-invasive subclinical vascular changes related to arteriosclerosis.

Pulse wave velocity (PWV) has also been evaluated as a measure of arterial stiffness. In hypertensive adults, the increasing PWV seen with stiffer vessels is strongly associated with presence of atherosclerosis *(137)*. Increased PWV adjusted for other cardiovascular risk factors was also the best predictor of cardiovascular mortality in this large adult study *(137)*. In asymptomatic young adults in the Bogalusa Heart Study, blood pressure is strongly related to aorto-femoral PWV (Fig. 14) *(138)* and was the first covariate to enter models exploring predictors of PWV *(139,140)*. While both systolic blood pressure and mean arterial pressure were important in explaining large and small artery compliance *(140,141)*, even more important is the observation that childhood systolic blood pressure is an independent predictor or brachial-ankle PWV as an adult *(142)*. Similar to results in carotid stiffness, candidate genes associated with blood pressure regulation appear to influence central aortic stiffness. Values for aorto-femoral PWV were significantly higher in subjects who were homozygous for the Glyc 389 polymorphism of the beta-adrenergic receptor gene even after adjustment for baseline levels of cardiovascular risk factors *(143)*. Racial differences were also apparent with the Arg 16 allele (vs glycine) associated with PWV only in African-Americans *(143)*.

In addition to abnormalities in arterial function, structural changes have been demonstrated in young, asymptomatic Bogalusa Heart Study participants. In correlation analyses, thicker intima–media thickness (IMT) of all segments of the carotid artery (common, bulb and internal) was related to higher blood pressure levels. This association retained significance in multivariate analyses for the common carotid artery and bulb *(144)*. In fact, systolic blood pressure was the first risk factor to enter models in stepwise analyses examining

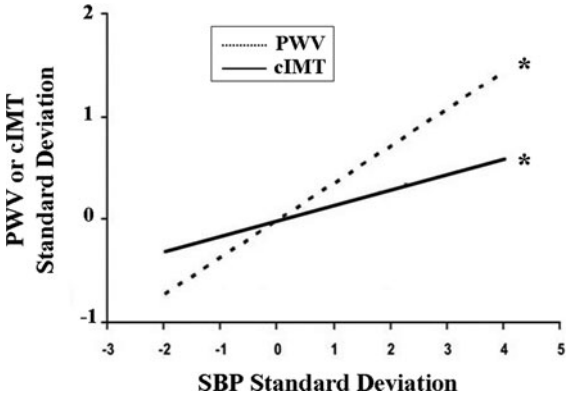

Fig. 14. Relationships of systolic blood pressure (BP) to aorto-femoral pulse wave velocity (PWV) and carotid intima–media thickness (cIMT). *The Bogalusa Heart Study* (N=900, standardized regression coefficient: PWV = 0.36, IMT = 0.15, $^*p$ for both $p \leq 0.01$) *(138)*.

independent determinants of carotid *(140)* and femoral IMT *(145)*. Systolic blood pressure measured in adult men was also a predictor of progression of a composite IMT measure in longitudinal studies after only 5.8 years of follow-up *(146)*. The influence of blood pressure on carotid IMT may be modulated by genetic factors. Only non-carriers of the G allele for the G-6A polymorphism of the angiotensinogen gene demonstrated a significant adverse association between higher mean arterial pressure and thicker common carotid IMT *(147)*.

Risk factor levels were also examined with subjects stratified by carotid bulb *(148)* or femoral *(149)* IMT. Subjects in the top fifth percentile for IMT were significantly more likely to be hypertensive or taking blood pressure-lowering medications compared to subjects with a normal carotid or femoral thickness (bottom fifth percentile). They also were more likely to exhibit abnormalities in other risk factors. The impact of clustering on IMT is evident as increasing numbers of CV risk factors (higher systolic blood pressure, cigarette smoking, higher total cholesterol to HDL cholesterol ratio, greater level of obesity, and higher insulin levels) or higher Framingham Risk Score was also associated with a linear increase in carotid IMT (Fig. 15) *(144,150)*. Subjects fulfilling the criteria for a diagnosis of metabolic syndrome with either the World Health Organization or the US National Cholesterol Education Program were found to have a thicker common and internal carotid IMT than subjects without metabolic syndrome *(151)*. Emerging data are now available relating cardiovascular risk factors such as elevated blood pressure to carotid thickness even in asymptomatic youth *(152)*. Bogalusa data also demonstrate that childhood SBP was independently related to adult carotid IMT *(153)*. Taken together, these data indicate the need to treat blood pressure at a young age almost as a continuous variable (rather than using a cut point) to prevent target organ damage.

Renal Dysfunction

Urine microalbumin excretion may result from increased intraglomerular pressure as a result of hypertension, thus serving as one of the best markers for subtle, asymptomatic chronic renal disease. In diabetic subjects, urine protein correlates with blood pressure levels *(154)*. Even in healthy young individuals, there is a significant and positive relationship between urine albumin excretion and systolic and diastolic blood pressure, especially in African-Americans (Fig. 16) *(155)*. Furthermore, in African-Americans with diagnosed

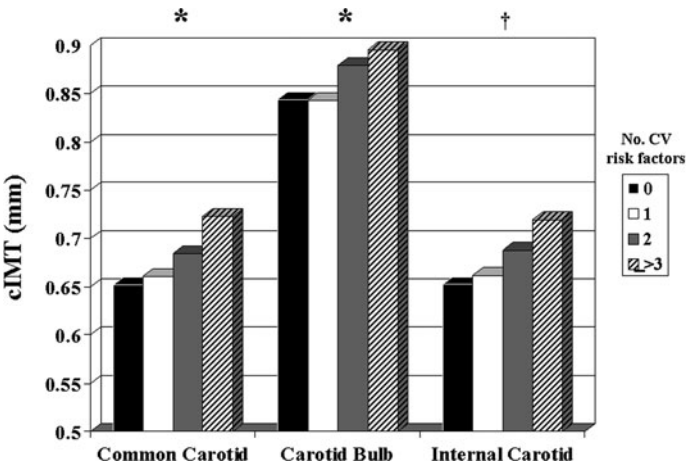

Fig. 15. The effect of multiple risk factors (total cholesterol to HDL cholesterol ratio, waist circumference, systolic blood pressure, insulin level >75th percentile specific for age, race, and gender, smoking) on carotid intima–media thickness (cIMT) in young adults. *The Bogalusa Heart Study* (N=518, $^*p \leq 0.0001$ for common and bulb, †trend for internal carotid p=0.09) *(144)*.

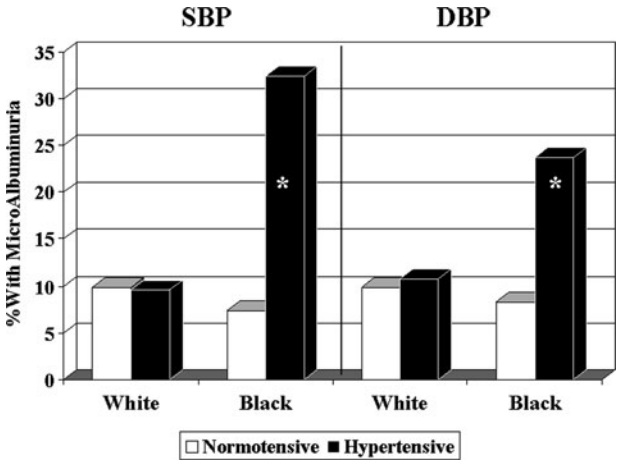

Fig. 16. Percentage of young adults with microalbuminuria by race and blood pressure classification. *The Bogalusa Heart Study* (N= 1131, $^*p$ for difference between normotensive and hypertensive African-American subjects is ≤0.01) *(155)*.

hypertension, elevated urine albumin excretion occurs with greater frequency than those considered normotensive *(155)*. These associations were not significant in whites and it has been postulated that African-American individuals may be more susceptible to renal damage from relatively low levels of blood pressure increases *(155)*. Subclinical hypertension-related renovascular disease can also be evaluated with measures of urinary activity of *N*-acetyl-β-D-glucosaminidase (NAG), which is elevated even in asymptomatic young people as systolic blood pressure levels increased (4 mmHg from lowest to highest quintile) *(156)*. This effect was strongest in African-American women *(156)*. Again, these observations point to the fact that subclinical kidney damage occurs with hypertension defined by task force guideline cut points and may even occur at lower levels. Furthermore, the effects are more extensive in African-Americans.

Results of Intervention

No longer are hypertension and coronary heart disease thought of as diseases of adults. The studies described above clearly prove that hypertensive disease and atherosclerosis begin in youth. It is paramount to begin prevention efforts early to obtain maximum benefit and attempt to break the viscous cycle of developing hypertensive cardiovascular disease. Physicians should encourage screening of high-risk groups in addition to promoting a population-based approach to achieving healthy lifestyles.

Guidelines for identifying and screening high-risk families should be followed by measuring risk factor levels of all family members. Unfortunately, even if previously informed that they were hypertensive, only 64% of Bogalusa Heart Study participants were aware of their condition at follow-up 5 years later and only 25% of self-reported hypertensives were receiving treatment *(157)*. Primary care practitioners should implement both primary and secondary prevention measures at all health-care encounters *(11,158,159)*. If lifestyle modification as the initial therapy for hypertension in a child fails, behavior change combined with low-dose medication will likely prove to be both safe and effective *(11,160–162)*.

Population-based models of prevention also have been proven effective. The DASH diet in adults shows lifestyle changes can help modulate blood pressure levels in a population broadly *(163)*. The efficacy of this diet intervention in youth has now been demonstrated *(164)*. Public health approaches to prevention of heart disease also have been developed such as The Health Ahead/Heart Smart Program which was developed as an outgrowth of data collected from the Bogalusa Heart Study *(165)*. This is a coordinated and comprehensive health education program, for kindergarten through sixth grade, addressing the entire school, community, and home environment. Traditional classroom training in health-promoting behaviors is combined with education in nutrition and physical activity in a non-competitive setting. School workers are taught healthier cooking methods while parents and teachers as role models are encouraged to engage in healthy lifestyles. Family and community support are encouraged through free screenings at 'health fairs' where nutrition and exercise are promoted as family lifestyles. Studies have proven the effectiveness of these programs in changing adverse health habits in both children and adults leading to measurable decreases in blood pressure levels in parents *(166,167)*. This program of educating children to become more aware of the need to take care of their own health

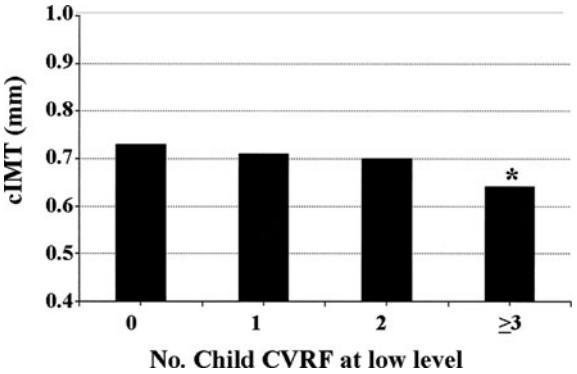

Fig. 17. Average (common, bulb, and internal) carotid intima–media thickness (cIMT) measured in adults by the number of CV risk variables at the bottom quartiles in their childhood. *The Bogalusa Heart Study* ($N = 1474$, $^*p$ for trend $= 0.013$) *(169)*.

has implications for physicians to provide leaderships to bring this message to their own communities *(168)*. The efficacy of primordial prevention (prevention of the acquisition of cardiovascular risk factors) is evident in data demonstrating lower adult carotid thickness in Bogalusa subjects who had multiple cardiovascular risk factors clustering at low levels in childhood (Fig. 17) *(169)*.

SUMMARY

It is clear that hypertension with target organ damage begins in youth. Hypertension is a complex syndrome mediated by multiple mechanisms and lifestyles. Proven methods for primary prevention should be a major goal for all health professionals along with more aggressive management of elevated blood pressure in early life.

ACKNOWLEDGMENTS

The authors wish to acknowledge the children and families in Bogalusa who made this research possible. The joint effort of the many individuals who have contributed to this study is gratefully acknowledged.

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12 Epidemiology of Cardiovascular Disease in Children

Samuel S. Gidding, MD

Contents

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, and 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 both as independent risk factors and are intimately related to the development of cardiovascular risk in adults (Table 1).

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_12
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Table 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

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, which is the prevention of the development of risk factors in the first place, and primary prevention, which is 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- to 34-year-old men and women dying accidentally. Lesions were graded according to the standard American Heart Association classification ranging from grade I (fatty streaks) to grade V (obstructive plaques). These pathologic measurements were related to risk factors measured postmortem: height and weight, serum measures (lipids, thiocyanate, glycohemoglobin), renal artery thickness (a surrogate for blood pressure), and other physical measures such as panniculus thickness.

The major findings of the PDAY study were that atherosclerosis is present in adolescents and young adults, that the severity of atherosclerosis increases rapidly so that by early adulthood advanced lesions (American Heart Association grades IV and V) are present, that the major risk factors are strongly related to atherosclerosis at all ages, and that the

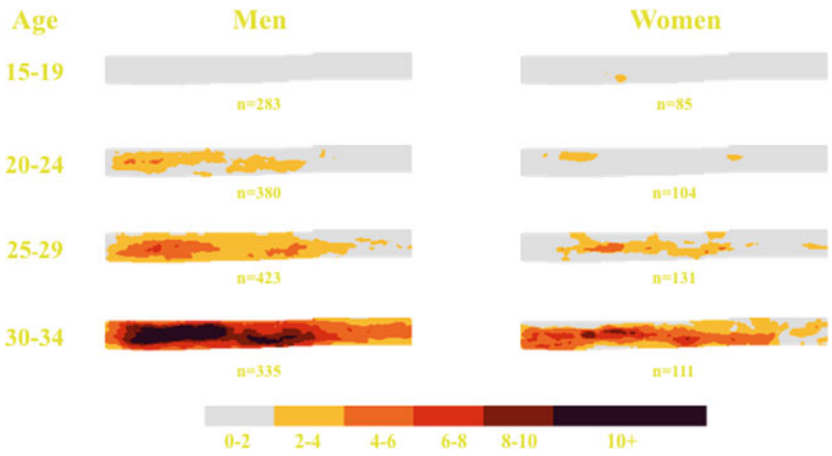

Fig. 1. Prevalence map of raised lesions of right coronary arteries by age and sex.

progression of atherosclerosis to more advanced lesions is related not only to the major risk factors but also to the presence of multiple risk factors simultaneously *(2)*. Atherosclerosis in women develops at a pace lagging about 5–10 years behind that in men (Fig. 1). Since most of the general population has at least one risk factor, the importance of public health measures and healthy behaviors in the prevention of atherosclerosis is a natural corollary of the PDAY findings. This is particularly true for children and adolescents when lesions are in the earliest and reversible phase (American Heart Association grades I and II) *(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 the abdominal aorta *(4)*.

Both non-HDL cholesterol and HDL cholesterol were related to atherosclerosis, both in the coronary arteries and in 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)*.

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 *(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 addictive, 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)*.

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

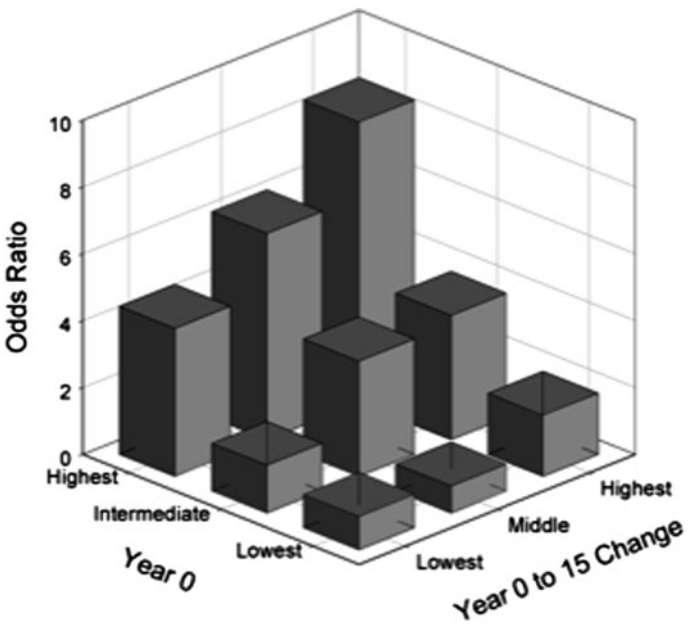

Fig. 2. The likelihood of having coronary calcium on CT scan at age 33–45 years is shown by the height of the bars. The groups are defined by tertiles of risk at baseline and change in risk over 15 years. As risk at baseline increases (higher PDAY risk score), likelihood increases. Risk change also impacts change in likelihood of future presence of coronary calcium.

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 better than risk factors measured at the time of the subclinical atherosclerosis measurement *(13–16)*. 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 the initial measurement and the time of subclinical atherosclerosis assessment added predictive ability *(16,17)*. Thus, improvement in risk as a young adult prevented acquisition of subclinical atherosclerosis (Fig. 2).

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 *(18)*. Cholesterol levels have a similar tracking coefficient *(19)*. 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 the age of 30–34 years, and young adults with a low PDAY risk score have minimal subclinical atherosclerosis *(3,16)*. Individuals who reach the age of 50 years and have no major cardiovascular risk have a lifetime risk of cardiovascular disease up to 95 years of age of 5% *(20)*. Maintenance of a low cardiovascular risk state is highly protective against atherosclerosis-related morbidity.

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 *(21,22)*. Animal models of atherosclerosis provide complementary data where the introduction of risk above threshold levels produces disease *(23)*. If one considers risk distribution of generally healthy non-obese children, the vast majority, probably greater than 90%, have risk thresholds associated with no adult cardiovascular morbidity *(24–26)*. 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 *(1)*. For example, in heterozygous familial hypercholesterolemia, 28% of children have coronary calcium present on CT scans *(27)*. 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 *(28,29)*. These children may benefit from aggressive risk factor reduction initiated at an early age. Although 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

Recognition of abnormal lipid levels, particularly LDL cholesterol, has been advocated by consensus groups since the release of the 1992 NHLBI National Cholesterol Education Program Report on cholesterol and children *(30)*. Revised guidelines have been recently developed that include recommendations with regard to triglycerides, HDL cholesterol, and non-HDL cholesterol. Table 2 presents the classification of lipid levels for children from the new 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 *(2,31)*.

Table 2
Lipid Classification for Children and Adolescents (in mg/dl)

	Acceptable	*Borderline*	*High*
Total cholesterol	<170	170–199	≥200
Non-HDL cholesterol	<120	120–144	≥145
LDL cholesterol	<110	110–130	≥130
Triglycerides ≤ 9 years	<75	75–100	≥100
> 10 years	<90	90–130	≥130
	Acceptable	Borderline	Low
HDL cholesterol	≥45	40–44	<40

For US children, NHANES III provides a distribution of lipid levels. Fasting values are available for adolescents in that study *(26)*. There is 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 *(32)*. 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 *(33)*.

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)*. 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 plasmapheresis to lower lipid levels. Hypothyroidism and nephrotic syndrome must be excluded in the presence of significant elevations of LDL cholesterol.

Fasting triglyceride levels above 150 mg/dl in a lean child or above 200–250 mg/dl in an obese child suggest an inherited disorder of triglyceride metabolism or familial combined hyperlipidemia. Homozygotes with severe disorders of triglyceride metabolism have levels >1000 mg/dl and require diets with <10% fat to prevent pancreatitis *(34)*. 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 in 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 *(21)*. 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 *(35)*.

The initial treatment of dyslipidemia is dietary. Table 3 provides useful principles of diet management *(36,37)*. 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 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 *(38)*, the National Cholesterol Education Program of the National Institutes of Health, and the American Academy of Pediatrics. For elevated triglycerides (below 750–1000 mg/dl), weight management is initial treatment. Avoidance of carbohydrates, particularly refined sugars, is critical. Avoidance of mono- and polyunsaturated fats

Table 3
American Heart Association Pediatric Dietary Strategies for Individuals >2 Years of Age

- Balance energy intake with energy expenditure to maintain normal growth
- Engage in 60 min of moderate to vigorous physical activity daily
- Emphasize deeply colored vegetables and fruits in the diet
- Substitute vegetable fats low in saturated fat and *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 non-fat dairy products on a regular basis
- Consume fish, especially oily fish, at least twice a week
- Reduce salt intake

is not necessary as they may be useful in maintaining or increasing associated low HDL cholesterol.

Pharmacologic treatment for elevated cholesterol is considered in children over 10 years of age with LDL cholesterol ≥190 mg/dl and failed dietary management. Statins are the initial management, and the goal of treatment is an LDL cholesterol <130 mg/dl. Liver function should be monitored and treatment is held for elevation of transaminases greater than three times normal. The presence of myalgia is an indication for witholding treatment as rhabdomyolysis can occur as a rare complication. Statins are not to be given during pregnancy or with breastfeeding. In children less than 10 years of age, statins can be considered in very high-risk settings. Randomized trials of statin treatment of up to 2 years duration have been reported *(39)*. 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 *(40,41)*.

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) *(42)*. 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 *(43)*.

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. In the United States, after years of decline, adolescent tobacco use spiked reaching a peak in the mid- to late 1990s. Since then, tobacco use declined until about 2002–2003, with about 15% of high school students currently describing themselves as regular smokers. 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 *(44)*.

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 *(45)*. Cigarettes, because of nicotine, are highly addictive. It is estimated that smoking 100 cigarettes or less may be sufficient to become an addicted smoker. Although randomized trials suggest physicians can be effective in smoking cessation treatment, success rates are low, particularly in youth. Pharmacologic treatments are available but there is limited published experience in youth. Although 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 *(46)*. Since most pediatric health-care providers are inexperienced in smoking cessation treatment, referral to a smoking cessation program or telephone quitline should be considered.

DIABETES MELLITUS

In adults, diabetes mellitus is considered a vascular disease equivalent *(21)*. 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 *(47)*.

The prevalence of both type I and type II diabetes mellitus is rising, the latter because of the obesity epidemic. In adolescents type II diabetes mellitus is now almost as common as type I *(48)*.

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 *(42)*. Studies in adults suggest that significant cardiovascular event reduction rates, similar to those in non-diabetics, can be achieved with hypertension and lipid lowering treatment *(21)*.

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 *(49)*. 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 it is associated with premature adult morbidity *(50)*. Establishing a pediatric definition has been difficult because of the dynamic nature of risk factors during youth *(35)*. Nonetheless, the prevention of obesity development in at-risk infants and children and the prevention of worsening obesity in affected children and adolescents are an important part of regular pediatric practice as at least one-third of US children are overweight or obese.

Family history remains an independent risk factor for atherosclerosis *(51)*. In adults, a positive family history increases risk even after control for potential genetic traits. Positive

family history predicts risk in offspring; conversely risk in childhood predicts risk in related adults. Family history independently predicts the presence of subclinical atherosclerosis *(52,53)*. 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- to 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 *(54)*. A diet low in salt is associated with lower blood pressure *(55)*. Although 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 *(36)*. 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 *(56,57)*. It is likely that an above average level of activity reduces the rate of rise of blood pressure over time *(58)*.

Socioeconomic status plays an important role in the evolution of cardiovascular disease risk, particularly with regard to behavioral factors *(59,60)*. Risk factor rates, particularly obesity-related co-morbidities 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 have been acquired in Caucasian populations, particularly male. Although 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 *(61)*. The prevalence of specific risk factors also varies by ethnic group *(62)*. Thus, more research is necessary before cardiovascular disease prevention recommendations can be made more specific for particular cultures.

NON-TRADITIONAL 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, it remains controversial whether or not these non-traditional risk factors substantially improve risk prediction beyond that provided by the

major risk factors described previously in this chapter *(63)*. Although 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 *(64)*. 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. Calcium does not enter atherosclerotic lesions until young adulthood, and normal values for cIMT are age and operator dependent and have not been established *(64)*. 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)*.

In adults, the best studied marker of inflammation is c-reactive protein; others include various vascular adhesion molecules and inflammatory cytokines *(67)*. There are very little pediatric data on these factors and for many, pediatric levels may be different than in adults. There is no 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 the major risk factors *(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 *(69)*.

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

13 Perinatal Programming and Blood Pressure

Julie R. Ingelfinger, MD

Contents

INTRODUCTION AND CONCEPTUAL BACKGROUND

Epidemiologic studies published in the late 1980s by Barker and his group *(1,2)*—and since replicated in a number of populations—provide evidence of an inverse relationship between birth weight and risk of cardiovascular disease, hypertension, renal dysfunction, and other diseases in adult life. Both clinical studies and a number of animal models have been used to investigate mechanisms underlying these observations [as cited in recent reviews *(3–6)*]. The concept that changes in the intrauterine milieu affect the growing fetus resulting in alterations in physiology and general health in later life has been termed perinatal programming or, more recently, developmental origins of health and disease (DOHaD). Yet, despite an increasingly complex literature about this phenomenon and its relationship to cardiovascular disease, the involved mechanisms remain elusive.

Nephron number is thought to influence blood pressure as well as susceptibility to renal disease in later life. Brenner et al. *(7)* were among the first to hypothesize that nephron number might influence the propensity to develop hypertension. A number of clinicopathologic observations suggest that such a relationship exists more directly. For example, Keller et al. *(8)* reported fewer nephrons in a small cohort of hypertensive adults who died in accidents as compared to the nephron number in normotensive persons who had similarly succumbed. The nephrons among the hypertensive subjects in the study were also larger than those in

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_13
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the normotensive group. Whether these observations would hold in other studies was not known until recently, when Hoy et al. confirmed such changes in a multiracial autopsy series. Hoy et al. suggest that a relatively larger mean glomerular volume and variation in glomerular volume within a kidney are markers of "glomerular stress" *(9)*. However, there may be ethnic and racial differences in that Hughson et al. *(10)* found no relation between blood pressure and glomerular number in American blacks.

A decreased nephron number may be associated not only with hypertension but also the tendency to develop chronic kidney disease. For example, Cass et al. *(11)* reported an association between low birth weight, hypertension, and later renal disease.

A growing body of laboratory work supports the concept that perinatal programming is linked to maternal malnutrition *(3,4,12–15)*, dietary deficiencies (e.g., retinoic acid) *(16)*, or exposures to certain substances during gestation (e.g., glucocorticoids) *(17)* that result in subtle alterations that cause offspring to have a propensity to develop high blood pressure or renal dysfunction after they reach adult life (Table 1). For example, numerous studies indicate that pregnant rats or guinea pigs administered low-protein diets during gestation produce offspring with relatively low birth weights, a propensity to have elevated blood pressure at maturity and deficient nephrogenesis *(3,4,12–15,18–21)*. The hypertension in such experimental models is often observed early and appears to persist, unless treated, throughout life. This chapter focuses on human data concerning the relation between perinatal programming and hypertension in later life.

Table 1
Maternal Factors Influencing the Risk of Future Hypertension

Maternal extrinsic exposures in the perinatal period and offspring hypertension
Protein-calorie malnutrition
High-salt diet
Iron deficiency
Vitamin A deficiency
Nephrotoxic drugs
Maternal intrinsic conditions in the perinatal period and offspring hypertension
Gestational diabetes
Maternal CKD

CLINICAL OBSERVATIONS ON PROGRAMMING AND BLOOD PRESSURE IN CHILDREN

In an early study of perinatal programming Barker et al. examined BP in 9,921 ten-year-old children in whom birth weight was available and observed that systolic blood pressure was inversely related to birth weight *(22)*. Law et al. *(23)* and Whincup et al. *(24)* also reported a direct relationship between birth weight and BP in children, an effect that seems definite, if small *(25–27)*.

Renal function in later life has also been inversely associated with birth weight. For example, the Nord Trøndelag Health 2 (Hunt 2) study *(28)* reported that persons born at term with relatively low birth weights had relatively lower glomerular filtration rate (GFR)

when examined at 20–30 years of age. There are also data suggesting that it is gestational age rather than birth weight per se that is important. For example, Siewert-Delle and Ljungman *(29)* observed that gestational age rather than birth weight itself was associated with both systolic and diastolic BP in middle-aged men. Their study *(29)* suggested that middle-aged men who had been term infants had BP that related to their adult BMI, not to birth weight alone.

Evaluating the effect of birth weight on adult blood pressure has not been feasible in prospective studies that track participants from birth to adult life. However, in a systematic review of more than 444,000 male and female subjects ranging in age from infancy to 84 years of age published in 2000, Huxley and her colleagues *(30)* reviewed 80 studies and drew the conclusion, based on their analysis, that birth weight is indeed inversely related to later systolic blood pressure levels. However, they also concluded that other factors, particularly the rate of postnatal growth, are influential in determining blood pressure *(25)*.

Thus, because variables other than birth weight exert major influences on BP in children, as well as on BP in adolescents and adults, the inverse relationship between birth weight and later BP level is not evident in all studies. The effect of current weight may outstrip the effects of birth weight. However, Seidman et al. *(25)* noted that birth weight had a lesser effect as compared to present weight. In data from the Bogalusa Heart Study, children with birth weights less than 2.5 kg at birth were compared to those weighing more than 2.5 kg; no association with birth weight and later blood pressure was discerned, likely owing to the effect of present weight *(31)*. In a study in 7-year-old children, Yiu et al. *(32)* found a positive effect of birth weight on hypertension once an adjustment for present weight at the time of follow-up was introduced.

The concept that deprivation during gestation results in a "thrifty phenotype" *(33,34)* in which the fetus is poised to take advantage of limited nutritional and environmental resources helps to explain why not all people exposed to adverse in utero conditions are equally affected. When postnatal environment provides surplus nutrients, as in Westernized and emerging nations, people metabolically programmed toward "thrift" are exposed to overabundance and are at high risk to develop hypertension and other health problems. Thus, the adiposity rebound that occurs may result in metabolic syndrome and its attendant cardiovascular risks.

EFFECTS OF ADVERSE GESTATIONAL CONDITIONS

Several situations that have been associated with perinatal programming will be now discussed in more detail. These include exogenous events such as protein-calorie malnutrition, vitamin A deficiency, exposure to exogenous glucocorticoids, high-salt diet, ethanol exposure, and iron deficiency. There are many intrinsic maternal conditions that influence the intrauterine milieu; some, such as maternal diabetes and placental insufficiency, have been shown to influence later cardiovascular function of the offspring.

Protein-Calorie Malnutrition

In human beings, it is generally difficult to quantitate the amount of nutritional alteration that occurs during gestation. However, there have been a few studies that have examined offspring born during famine, during which entire populations are subjected to marked protein-calorie malnutrition. For example, the children of women who were pregnant during the Dutch Famine, which took place in the western part of the Netherlands in 1944–1945, have been a well-studied cohort. During the Dutch Famine, caloric intake per person

was below 900 kcal/day for several months. The most complete reports *(35,36)* concerning the offspring of mothers subjected to this famine include 724 people (all singletons) born during the last months of World War II; they were 48–53 years old at the time of study. Interestingly, the urinary albumin excretion was increased in 12% of the cohort who had been exposed in utero to famine during mid-gestation (adjusted odds ratio 3.2, with 95% CI 1.4–7.7). These survivors had a higher likelihood of hypertension as well. Persons exposed to famine while in utero in the first and last trimesters of pregnancy had other increased risks. Thus, the time during gestation in which the famine occurred was important.

Children whose mothers were pregnant during another famine during World War II, the Siege of Leningrad, have also been studied. Yudkin et al. *(37)* studied 98 people whose mothers had been exposed to marked protein-calorie nutrition during that siege. The investigators measured microalbuminuria in these survivors and compared the results to those of 124 persons who had been infants in Leningrad during the siege but whose mothers had not been subjected to famine while pregnant and to 62 Russians of the same age who lived outside the area of the siege while it was ongoing. The investigators also compared these results to those of 236 residents of Preston, UK, who were of the same age. Only 11 people had microalbuminuria, and there were not statistically significant correlations between in utero starvation, birth weight, and microalbuminuria.

In sum, there is not strong evidence to directly or indirectly link human maternal low protein-calorie intake to hypertension. Further, there is no clear evidence that protein and calorie intake per se influence nephron number or renal size in humans.

Vitamin A Deficiency

For many years it has been known that vitamin A deficiency and a number of birth defects, including renal anomalies, are associated *(14,16,38–46)*. However, there are suggestions that mild vitamin A deficiency may be associated with subtle renal defects. While animal studies support this concept, and while retinoic acid may correct the defect in vitro *(44)*, proof in humans is difficult.

Goodyer et al. *(45)* noted that kidneys at birth are smaller in children from Bangalore, India, as compared to the kidneys of babies in Montreal. They observed that vitamin A levels in the mothers from India were lower than those of mothers in Montreal. See a recent Cochrane review for discussion of the effects of vitamin A supplementation in humans *(46)*.

Glucocorticoid Exposure

A number of studies in animal models indicate that exposure to exogenous glucocorticoids during pregnancy acts as a negative modifier of renal development, possibly resulting in higher risk for hypertension and other disease later in life *(17,47–51)*.

Glucocorticoids are used clinically, for example, to promote lung maturation in anticipated premature delivery; some follow-up data are available. One observational study of 14-year-old children who had been exposed to betamethasone in utero found higher BPs in those youngsters as compared to normal; however, the study may have been confounded by puberty, given the age of the subjects *(52)*. In another study, a small, randomized trial, systolic blood pressure was less at age 20 in young people who had been exposed to betamethasone in utero as compared to those not so exposed *(53)*.

Dalziel et al. *(54)* studied children whose mothers had taken part in a randomized study during which they had received betamethasone or placebo during pregnancy. At age 30, the now-grown children underwent examination of their blood pressure, body indices, as

well as glucose tolerance, lipid status, and plasma cortisol. There were no differences in body size, BP, or cardiovascular disease in those exposed or not exposed while in utero. However, the offspring whose mothers had received betamethasone during gestation had a higher frequency of dysglycemia as measured by glucose tolerance testing.

In a multicenter study *(55)* Finken et al. evaluated 412 former premature infants (born at 32 weeks of gestation) at 19 years of age. Some participants had been born to mothers who had received two doses of betamethasone (12 mg) to induce lung maturation. There were no differences in serum lipids and insulin resistance between the groups. While estimated glomerular filtration rate (eGFR) was normal in all subjects, it was significantly lower among those subjects whose mothers had received steroids (mean ± SD = 103.5 ± 12.6 ml/min/1.73 m^2, betamethasone group vs. 107.0 ± 15.6 ml/min/1.73 m^2, control group).

High-Salt Diet

Increasing maternal salt intake can result in changes in renal structure and function quite similar to those produced by protein restriction *(56–58)*. Since increased salt intake by itself decreases fetal RAS expression, it would appear that a similar mechanism is operative.

Gestational high salt intake in animal models is associated with hypertension in offspring. Swenson et al. *(59)* observed that Sprague-Dawley rats that received a high-salt diet in the perinatal period later become hypertensive. Their work indicates that the high blood pressure is associated with increased central nervous system AT_1 receptor activation, leading to increased sympathetic nervous activity. In contrast, Vidonho et al. *(60)* reported that perinatal restriction of salt also had later adverse events.

The data concerning the perinatal effects of salt intake in humans are limited. However, Simonetti et al. *(61)* reported that children with low birth weight had increased salt sensitivity and increased responsiveness of blood pressure to changes in the salt in the diet *(62)*.

Ethanol and Renal Development

While much is known about adverse effects of ethanol on the developing brain, little has been studied in terms of its effect on renal development. Gray et al. *(63)* examined the effects of multiple exposures to ethanol in the sheep model. They observed an 11% reduction in nephron number, though the overall kidney growth and the size of the fetus were not changed. Additionally there were no changes in gene expression so far as examined.

While some children with fetal alcohol syndrome have been reported to have kidney malformations—with small kidneys with malrotation and other anomalies—little is known about the relation between maternal alcohol intake during gestation and future cardiovascular health *(64–66)*.

Iron Deficiency

Iron deficiency during pregnancy in experimental models has been shown to result in offspring with hypertension. For example, Lewis et al. *(67)* found that restricting iron intake in the pregnant rat led to decreased birth weight in the pups and subsequent hypertension in adult life. Iron-restricted mothers were anemic at delivery, and their pups had lower hemoglobin levels as compared to normal offspring. At 3 months of age offspring remained anemic, and their systolic BP was elevated compared to BP in offspring of mothers that had not been iron restricted. Iron-restricted offspring had decreased fasting serum triglyceride

levels, though fasting serum cholesterol and free fatty acid concentrations were similar in both groups. Insulin levels were not different between the groups. Thus, maternal iron restriction seemed to "program" offspring for future hypertension, with findings reminiscent of the maternal protein restriction model. Lisle et al. extended this work, with results suggesting a deficit in nephron number *(68)*. Subsequent work by Andersen et al. suggested that the adverse effects of maternal iron deficiency, studied with cultured rat embryos, could be rescued by restoration of iron in media *(69)*.

Iron deficiency is very common in pregnant women, even in industrialized nations *(70)*. Some studies have shown positive relationships between maternal hemoglobin and anemia *(71,72)*, while others have found no associations *(73,74)* and still others an inverse association *(75)*. Brion and colleagues *(76)* examined maternal anemia, iron intake during gestation, and blood pressure at age 7 in the Avon Longitudinal Study of Parents and Children. They found no effects, once data were adjusted for age, sex, and other confounders. If anything, blood pressure was lower in the offspring of anemic women.

PREMATURE BIRTH AND LATER BLOOD PRESSURE

Premature birth may occur prior to the completion of nephrogenesis *(77)*. Recently Gubhaju et al. *(78)* examined a primate model and found a high proportion of abnormal glomeruli in some but not all kidneys when animals were delivered at 125 days of gestation. There was no influence induced by providing glucocorticoids antenatally. The implications of their work to humans are not known at this time.

We do know that premature infants born early yet not surviving the neonatal period have hypertrophied glomeruli *(79)*. Further, premature infants of extremely low birth weight surviving into mid-childhood have been reported to have an increased amount of proteinuria *(80)*. Recently Hodgin et al. *(81)* reported that extremely low birth weight was a risk factor for secondary focal segmental glomerulosclerosis. Kistner et al. *(82)* examined blood pressures in women who had been born preterm and noted that there was a relative increase in systolic blood pressure as compared to those born at term.

POSSIBLE MECHANISMS OF PROGRAMMING

What are the mechanisms underlying the clinical and laboratory observations that perinatal events influence later cardiovascular and renal function? The coordinated developmental events involved in organogenesis are extremely complex *(3–6)*. It has been recognized for many years that toxic events that interrupt gestation can lead to such disordered development that a fetus does not survive *(3–6,83,84)*. For decades, toxicologic studies have constituted a major portion of new drug development, as well as a major medicolegal focus whenever a medication produces serious fetal abnormalities. In contrast to the effects of known toxins, the insults incurred by the fetus due to malnutrition do not generally produce clearly visible or identifiable abnormalities at birth.

To date, there have been several approaches to seek mechanisms responsible for perinatal programming. First, candidate genes and systems have been examined, most notably, to search for changes in steroid metabolism and feedback systems and to seek alterations in vasoactive systems such as the renin–angiotensin system, which are known to impact organogenesis and repair, and changes in biological systems that might lead to fibrogenesis.

Altered Steroid Metabolism

A number of observations support the idea that alterations in steroid metabolism can be caused by maternal diet and medication that can lead to changes in renal structure and function *(85)*. For example, protein restriction decreases the amount of placental 11β-hydroxysteroid dehydrogenase. Decreases in this enzyme, which inactivates maternal cortisol or corticosterone, lead to increased fetal exposure to glucocorticoids from the mother *(17)*. Such increased exposure may lead to steroid actions on nuclear receptors that might well influence the development of the kidney and vasculature. Infants with lower birth weight have been found to have placentas with relatively low 11β-hydroxysteroid dehydrogenase activity, supporting the concept that increased glucocorticoid exposure has been present *(51,85)*. This basic observation has led to the hypothesis that in conditions of low protein intake, placental 11βHSD is decreased, possibly leading to an increase in the amount of maternal steroids reaching the fetus with attendant changes in nephrogenesis. Indeed, dexamethasone administered to pregnant rats crosses the placenta yet is not metabolized by 11βHSD, leading to low birth weight pups with a propensity to become hypertensive as adults *(86,87)*. Carbenoxolone (an inhibitor of 11βHSD) also has resulted in low birth weight animals with a tendency toward hypertension in one study *(88)* but not in another *(89)*.

Alterations in Renal Tubular Transporter

Manning et al. *(90)* hypothesized that changes in the fetal kidney would program later inappropriate sodium retention in later life as one explanation for the hypertension observed. Thus, they examined the possible role of sodium transporters, speculating that at least one would demonstrate increased activity. Low-protein offspring showed evidence of upregulation of mRNA for two transporters, renal BSC1 and TSC at 4 weeks of age, prior to the development of hypertension.

Glomerular Hyperfiltration

Lucas *(91)* has reproduced the undernutrition model and examined in some detail what happens within hypertrophic glomeruli. In his model, dams subjected to 50% food restriction bore offspring with a decreased number of glomeruli that exhibited increased glomerular diameter, suggesting compensatory hypertrophy and hyperfiltration. He posited that glomerular hypertrophy would lead, ultimately, to renal damage and carried out morphologic, immunohistochemical, and functional studies in the offspring exposed to this energy restriction in utero. The offspring of restricted rats exhibited intense tubulointerstitial lesions and immunohistochemical alterations in the renal cortex—increased fibronectin and desmin expression in glomeruli and tubulointerstitium and increased vimentin and alpha-smooth muscle actin in the tubulointerstitial area from the renal cortex. Furthermore desmin was increased at the periphery of glomeruli, which implies likely podocyte injury. The investigators suggested that the aberrant glomerulogenesis in the offspring of the malnourished dams resulted in hyperfiltration and ensuing renal damage.

Alterations in the Renin–Angiotensin System

The intrarenal renin–angiotensin system (RAS) generally demonstrates altered expression in the offspring of mothers that have been subjected to protein restriction during gestation. The kidneys of rat pups born to protein-restricted mothers show dramatic decreases

in renin mRNA protein immunostaining and angiotensin II levels *(20,21)*. The decrease in intrarenal angiotensin II is of particular interest, since that octapeptide is critical to normal growth and remodeling and thus important in nephrogenesis *(92)*. However, taken together, these data suggest that interruption of normal functions of the RAS could result in fewer nephrons, ultimately predisposing to hypertension in adult life *(93)*.

The two sexes are not similarly prone to experience perinatal programming given the same exposures. Thus, programming exhibits sexual dimorphism *(94)*. For example, Holemans et al. *(95)* showed that male offspring of mothers that had been administered low-protein diets in the latter half of pregnancy were far more susceptible to low birth weights than their female littermates. The female littermates then appeared to be resistant to elevated blood pressure as adults. Woods et al. have also noted that male pups were more susceptible to decreases of intrarenal renin and angiotensin II; males, but not females later became hypertensive *(94)*.

Endocrine Alterations

Vickers et al. *(96,97)* have induced maternal undernutrition throughout pregnancy, followed by postnatal hypercaloric nutrition in offspring to produce a rat model of metabolic syndrome. They observed the development of hyperphagia, obesity, hypertension, hyperinsulinemia, and hyperleptinemia in those offspring whose mothers had been subjected to undernutrition in pregnancy. This model has also been used to study the influence of IGF-I administration.

Growth Factors and Inflammation

Growth factors are important in nephrogenesis, and their alterations may lead to aberrant renal morphogenesis *(92,98)*. Rees et al. *(99)* have demonstrated that maternal protein deficiency leads to maternal decrease in circulating threonine and is associated with hepatic hypermethylation of DNA.

Other Mechanisms

The coordinated program necessary for the formation of the kidney requires several development and regression of the pronephros and mesonephros and the interaction of the mesonephros with the metanephros *(100)*. The changes wrought in perinatal programming would be more than likely reflected by subtle alterations in the process of nephrogenesis. The hypothesis and observation that adult hypertension is associated with fewer nephrons have been well articulated by Brenner and Mackenzie *(101)*. Fewer glomeruli have been reported in autopsies of human infants with intrauterine growth retardation, which is consistent with that theory *(79)*. The work of Kwong et al. *(102)* observed increased apoptosis in blastocysts of rats exposed to a low-protein diet in the preimplantation stage of gestation. Welham et al. *(103)* reported that protein restriction during gestation in the rat appears to be associated with increased apoptosis in mesenchymal cells. Welham et al. *(103)* noted that the metanephric mesenchyme, a subset of which is induced to form nephrons, is derived from the intermediate mesoderm. The intermediate mesoderm is also the source of the pronephros and mesonephros, which eventually become residual structures such as the Wolffian duct. Metanephric mesenchyme that is recruited via factors emanating from the ureteric bud to form the final kidney will undergo apoptosis unless rescued. Thus, increased apoptosis would presumably result in fewer generations of nephrons.

Oxidative stress and subsequent inflammation may be important in programming hypertension during gestation and the perinatal period. Work by Stewart et al. *(104)* in the rat model of maternal low-protein diet indicates that the offspring have evidence both of oxidative stress and of inflammation. Treatment of animals with mycophenolate and also the superoxide dismutase mimetic tempol lessened immune cell infiltration and increased renal nitrotyrosine levels.

Epigenetic Influences

Certain congenital anomalies of the kidney and urinary system are the result of monogenic mutations inherited via classic Mendelian genetics *(105–107)*. Changes in nephron number do occur in some of these disorders, which involve renal dysplasia, hypoplasia, and malformations (see Chapter 6 and *(106)*). However, more subtle alterations via epigenetic marking may be involved in perinatal programming *(106,108)*. Epigenetic alterations occur via DNA methylation and histone modification of chromatin or via proteins that associate with DNA. Such epigenetic changes can result in changes in both gene expression and stem cell lineage *(108–110)*. DNA-binding factors such as *Pax2* and *Pax8*, which are DNA-binding factors, are critical in renal development and have been proposed as means by which histone modification in the developing kidney might take place *(110)*.

Sodium resorption is important in the development of hypertension, and alterations in the expression of sodium transporters have been noted in offspring of dams subjected to protein restriction during gestation. Recently Zhang et al. reported that the collecting duct epithelial sodium channel is subjected to epigenetic control *(111)*. Kaneko et al. have published a recent review about the possible roles of epigenetics in organogenesis *(109)*.

What do all of these observations tell us? Basic studies provide substantial evidence that intrauterine events affect nephrogenesis, perhaps in subtle ways, the effects of which can only be observed later in life *(112)*. The propensity to develop hypertension, renal disease, and cardiovascular disease may well be initiated, at least in some persons, by intrauterine and perinatal events that impact organogenesis in subtle ways.

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14 Familial Aggregation of Blood Pressure

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Contents

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 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, respectively, for systolic BP (SBP) and 0.32 and 0.17, respectively, 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

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_14
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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 and can take two different forms *(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, i.e., age-dependent gene expression.

Therefore, in this chapter we will review the available literature of 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 have been frequently 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 in BP of 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)*, whose applicability is somewhat limited due to 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 on the equal environment assumption (e.g., *(12)*), most studies specifically carried out to test it have proved it to be 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, and Tables 1 and 2 summarize pediatric and adult studies, respectively. Only twin studies with a reasonably large sample size (>50 twin pairs total) were included. Although studies used different methods to estimate heritability, it is immediately obvious from these tables that the evidence for a sizeable contribution of genetic factors to BP is overwhelming, with most heritability estimates around 50–60%. 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. *(19)* in which heritabilities of BP were estimated in more than 4000 twin pairs from six different countries. Heritabilities of DBP were between 44 and 66% across samples. For SBP, the range of estimates were even narrower between 52 and 66%. Shared environmental factors did 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 *(20–22)*. Another part of the story might be that many twin studies may lack the power to detect moderate size influences of common environment *(23,24)*. A few studies that either had large sample sizes *(25,26)* or used a more powerful multivariate approach *(27)* 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 autosomal genes are not expected to

Table 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. *(54)*[a]	274 MZ, 65 DZ	? (?)	0.0–1.0	Chinese	m and f	0.29–0.55	0.27–0.45
Levine et al. *(29)*[b]	67 MZ, 99 DZ	? (?)	0.5–1.0	b and w	m and f	0.66	0.48
Havlik et al. *(70)*	72 MZ, 40 DZ			Black	m and f	0.46	0.51
	43 MZ, 42 DZ			White	m and f	0.11	0.71
	115 MZ, 82 DZ	7.0 (?)	?	All	m and f	0.23	0.53
Wang et al. *(71)*	75 MZ, 35 DZ	? (?)	7.0–12.0	Chinese	m and f	0.32	0.46
Schieken et al. *(72)*	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. *(30)*	40 MZM, 47 MZF	14.0 (6.5)	5.0–50.0	b and w	Male	0.41	0.56
	32 DZM, 36 DZF, 45 DOS				Female	0.78	0.61

Table 1 (continued)

		Age				h^2	
Study	*Pairs of twins*	*Mean (SD)*	*Range*	*Race*	*Sex*	*SBP*	*DBP*
Snieder et al. *(31)*	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

Abbreviations: MZF = monozygotic females, MZM = monozygotic males, DZF = dizygotic females, DZM = dizygotic males, DOS = dizygotic opposite sex, b and w = black and white combined, m and f = males and females combined, ? indicates that age is not reported in the original paper.

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

[b]Heritability estimates reported by Levine et al. *(29)* were doubled as outlined by Kramer *(73)*.

Table 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. *(74)*	40 MZM, 45 DZM	19.4 (3.0)	?	White	Male	0.68	0.76
Ditto *(75)*	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. *(76)*	129 MZ, 66 DZ	21.3 (2.8)	18.0–30.0	94% White	m and f	0.48	0.51
Bielen et al. *(77)*	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. *(35)*	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. *(78)*	100 MZ, 66 DZ	29.8 (12.0)	?	White	m and f	0.74	0.72
Slattery et al. *(79)*	77 MZM, 88 DZM	? (?)	22.0–66.0	White	Male	0.60	0.66
Vinck et al. *(37)*	150 MZ, 122 DZ	34.9 (?)	18.0–76.0	White	m and f	0.62	0.57
Jedrusik et al. *(36)*	39 MZ, 37 DZ	35.0 (8.0)	18.0–45.0	White	m and f	0.53	0.62
Williams et al. *(80)*	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

Table 2
(continued)

Study	Pairs of twins	Age		Race	Sex	H^2	
		Mean (SD)	*Range*			*SBP*	*DBP*
Austin et al. *(81)*	233 MZF, 170 DZF	42.0 (?)	?	90% White	Female	0.35	0.26
Baird et al. *(53)*[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. *(26)*	213 MZF, 556 DZF	45.4 (12.4)	18.0–73.0	White	Female	0.17	0.22
Feinleib et al. *(82)*	250 MZM, 264 DZM	? (?)	42.0–56.0	White	Male	0.60	0.61
Hong et al. *(25)*	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

For abbreviations see Table 1.
[a]DBP heritabilities were not reported in the original paper.

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 *(28)*. Sex differences in magnitude of genetic and environmental effects can be tested by comparing parameter estimates between males and females. If studies considered sex differences in heritabilities, estimates for males and females are listed separately in Tables 1 and 2. However, heritability estimates for males and females are remarkably similar. A number of studies even report the same heritabilities for the two sexes, indicating that estimates for males and females could be set equal as part of the model fitting process used in these studies. Lower correlations in DZ opposite-sex pairs compared to same-sex DZ pairs indicate that genetic or shared environmental influences may differ in kind between males and females, but this has never been reported for BP.

Ethnic Effects on BP Heritability

Genetic as well as environmental differences between different ethnic populations may result in different BP heritabilities. As shown in Tables 1 and 2 most twin studies were conducted in Caucasian populations and a few combined twins from different ethnic groups without reporting separate heritability estimates *(29,30)*. 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 recently 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 *(31)*. Thus, concurrent with the few other twin studies of non-Caucasians as reported in Table 1, there seems to be no evidence for large differences in BP heritabilities between different ethnic groups. The fact that a similar amount of BP variation is explained by genetic factors within different ethnicities does not exclude the possibility; however, 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 real 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 *(32)*.

To circumvent disadvantages of conventional BP measures several twin studies have examined ABP, but the sample sizes of the initial studies have been small. Degaute et al. *(33)* evaluated 24-h ABP in a hospital research setting with 28 MZ and 16 DZ pairs of young adult males. The small sample size and the presentation of 33 different measures make interpretation of results difficult, but overall evidence suggested heritability on some characteristics of the 24-h profiles for DBP. Somes et al. *(34)* examined the heritability of ABP in 38 pairs of MZ twins, 17 pairs of same-sex DZ twins, and 11 pairs of opposite-sex DZ twins. Heritability estimates of 0.22 and 0.34 were observed for 24-h SBP and DBP, respectively. Fagard et al. *(35)* measured 24-h ABP in 26 MZ and 27 DZ male twin pairs aged 18–38 years. Using model fitting techniques, heritability ranged from 0.51 to 0.73 for 24-h, daytime, and nighttime SBP and DBP. The remaining variances were typically

accounted for by unique environment (range = 0.27–0.40). Jedrusik et al. *(36)* measured 24-h ABP in 39 MZ and 37 DZ twin pairs aged 18–45 years and observed that heritabilities for 24-h, daytime, and nighttime SBP and DBP ranged between 0.37 and 0.79.

More recently, three twin studies with relatively large sample size using ABP monitoring have been conducted. Vinck et al. *(37)* measured conventional and ambulatory BP in 150 MZ and 122 DZ pairs. Heritabilities were similar (around 50%) for laboratory and ambulatory (daytime and nighttime) SBP and DBP irrespective of the chorionicity of the MZ twins *(38)*. Kupper et al. *(39)* evaluated daytime ABP in 230 MZ and 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 years; range: 11.9–30.0 years) from the Georgia Cardiovascular Twin Study *(40)*. Inspired by evidence from prospective studies showing that nighttime BP is superior to daytime BP as a predictor of cardiac mortality *(41)*, 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. Our findings suggest that the underlying genetic mechanisms for BP regulation change with the day–night shift.

Nocturnal BP fall is another interesting feature revealed by ABP. Studies have shown that individuals with a blunted nocturnal decline in BP (the so-called nondipping) display the highest risk because this pattern exposes these individuals to a greater cardiovascular load each day. Fava et al. *(42)* 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 *(40)*.

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. In fact, 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. *(43)* 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. *(43)* did not elaborate on this, such an increase in genetic variance may 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 *(44)*. 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 *(44)*. This has clear implications for gene-finding studies. The genetic variation that emerges exclusively during stress can only be found 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.

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. *(45)* 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 *(46)* and females *(47)* 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 *(47)*.

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 reduces 1–2 mmHg for every kilogram increase in birth weight for children and the effect increases to about 5 mmHg/kg in elderly people *(48)*. 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. *(49)* 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 *(50)* 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 twins and 1.74 (95% CI: 1.13–2.70) for MZ twins, which suggests that the association between birth weight and the risk of hypertension is independent of both shared familial environment and genetic factors. On the other hand, there are also studies supporting the possibility that factors shared by twins confound the association between birth weight and blood pressure. For example, Christensen et al.'s study in 1311 pairs of adolescent twins found a decrease in SBP of 1.88 mmHg for every kilogram increase in birth weight in the overall sample, but a reduction of this effect was observed when intrapair analyses were used *(51)*. This was confirmed by a recent meta-analysis *(52)* in 3901 twin pairs in which the decrease in SBP for every kilogram increase in birth weight was –2.0 (95% CI: –3.2 to –0.8) mmHg in the unpaired analysis, but only –0.4 (95% CI: –1.5 to 0.7) mmHg in the paired analysis. Thus, the association between birth weight and SBP attenuated when familial factors were controlled for suggesting that 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 *(53)*.

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 age.

Cross-Sectional Studies

Twin Studies

In both Table 1 (mean age <18 years) and Table 2 (mean age >18 years), studies are listed in ascending order according to age of the twin sample. Such a systematic overview of all studies may reveal any age-dependent trends in heritability, because each study yields

heritability estimates representative of its specific age range. However, neither within the adult nor the pediatric age range can clear age trends in BP heritability be detected. Two studies in very young twins *(29,54)* confirm the conclusions from previously mentioned family studies that familial aggregation is established very early in life. These twin studies suggest that this can be ascribed to genetic factors. The above-mentioned study of Vinck et al. *(37)* specifically investigated 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, therefore, warranted that the relative influence of genetic factors on BP is stable across the life span.

Family Studies

Parent–Offspring and Sibling Correlations. Another approach to investigating the age dependency of genetic and environmental effects is to compare parent–offspring data with data from siblings or twins. If there is an age-dependent genetic or environmental effect on the phenotype, one would expect the parent–offspring correlation to be lower than sibling or DZ twin correlations, as the latter are measured around the same age. This expectation was confirmed in a review by Iselius et al. *(55)*. 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. *(56)*, who measured SBP and DBP for 1141 parent pairs aged 48–51 years. After 20–30 years, blood pressures for 2497 of their offspring were measured. At this time, the offspring were of ages similar to those of their parents when they 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 *(25,57)*. 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. *(56)* 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 *(55,57,58)*, while estimates from twin studies are typically in the 0.40–0.70 range for both SBP and DBP *(19)* (see also Tables 1 and 2).

Age-Dependent Gene Expression. Two types of age-dependent effect could offer an explanation for the lower parent–offspring correlation compared to the sibling and DZ twin pair correlations. First, the influence of unique environmental factors may accumulate over a lifetime. Such an increase, however, would lead to lower heritabilities with age, which is not supported by the evidence presented in Tables 1 and 2. Second, different genes could

influence BP in childhood and adulthood. This possibility is still compatible with the results of Tables 1 and 2, as heritability can remain stable across time even though different genes are influential at different times. The latter possibility is supported by data from Tambs et al. *(59)*. 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, ages 20 and 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. *(59)* 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 *(60)*, 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. *(59)* (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. *(61)* analyzed resting SBP and DBP in 254 MZ and 260 dizygotic (DZ) male middle-aged twin pairs (average age 48 years) and again 9 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 and no new genes were evident. 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 *(62)*. 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 *(63,64)* 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 cover the important transition from childhood to adulthood. We recently conducted the first longitudinal twin study on BP *(65)* 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 newly expressed genes between 14 and 18 years. 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 of 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, offered 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 causal mechanisms. There is a considerable tracking of BP levels from childhood to adulthood *(66)*, making BP at a young age an important predictor of adult levels *(67)*. 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 *(68,69)*.

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15 Influence of Dietary Electrolytes on Childhood Blood Pressure

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Contents

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 track from childhood to the third and fourth decades of life *(1,4)*, and elevated BP levels have been associated with increased risk of cardiovascular and renal diseases *(5)*. Hypertension and cardiovascular risk also increase with increasing rates of overweight and obesity, and prevention programs are needed to reduce these risks in youth *(5–7)*. Modifying intake of dietary electrolytes such as sodium and/or potassium has been shown to be an effective approach to BP reduction in adults *(8–10)*, but there is less evidence for the benefit of this approach in children and adolescents *(11)*. Current recommendations for primary prevention of HTN, published by The National High Blood Pressure Education Program Coordinating Committee *(12)*, involve a population approach and an intensive strategy for targeting individuals who are at increased risk for developing HTN in early adulthood. The Committee outlines a number of approaches that have proven effective for prevention of HTN. Two of these approaches include reducing sodium intake and maintaining an adequate intake of potassium. Evidence also suggests that addressing obesity-related hypertension through weight reduction and maintenance programs may be more efficacious when physical activity is incorporated into the intervention, and regular aerobic activity is strongly recommended for improving BP *(13–15)*.

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_15
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Identifying precursors or markers of HTN in youth is important for preventing the development of essential HTN. Two such markers include cardiovascular reactivity (CVR) and ambulatory BP profiles *(16–18)*. Cardiovascular reactivity is a measure of vasoconstriction in response to psychological or physical stressors. As a marker, hyperreactivity is conceptualized as a consequence of pre-existing 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 the development of 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 essential HTN *(17,19–23)*, although efforts to associate it with physiological correlates of HTN (i.e., left ventricular hypertrophy) have yielded mixed results *(16,24–27)*. Only a limited number of studies have been conducted examining the relationship between dietary electrolytes and CVR in youth, and the results of these studies have been inconsistent *(16)*.

Ambulatory BP profiles may be an important predictor or risk factor of future HTN in youth. Ambulatory BP (ABP) is a method for assessing an individual's 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 *(18)*. In healthy individuals, average BP declines by 15% or more during sleeping hours, while for hypertensive patients the circadian rhythm is generally preserved. The 24-h BP profile, however, is shifted upward to a higher magnitude throughout the 24-h period *(28)*. A number of studies suggest that a blunted nocturnal decline in BP may be associated with greater cardiovascular risk *(18)*. For example, ambulatory BP nondipping status (defined as <10% decrease in BP from waking to sleeping) is a risk factor for the development of end-organ disease in essential HTN. Specifically, patients who are characterized as nondippers show a more frequent history of stroke and left ventricular hypertrophy (LVH) *(29–31)*. Studies from our laboratory indicate that even among healthy African-American adolescents, there is a 30% prevalence rate of nondipping status *(32,33)*. These findings have led us to investigate the dietary electrolyte factors that may influence the ABP pattern in youth.

Previous research indicates that dietary factors such as sodium and potassium significantly affect BP in adults, especially in industrialized countries *(34–37)*. 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 *(38)*. Electrolyte balance (i.e., balance of positively and negatively charged conductive ions) is essential for health and affects the regulation of hydration, blood pH, and motor functioning *(38)*. Although some controversy exists about the differential effects of electrolyte intake on BP in childhood, some studies indicate that the relation between environmental and genetic factors influences BP responses in children *(39–42)*. Specifically, some investigators have demonstrated that children as young as 0–3 years of age may be at higher risk for future cardiovascular complications because of differences in sodium handling and genetic phenotypes *(43)*, and that stress-induced excretion is a heritable phenotype which differentially affects African-Americans as compared to Caucasians *(39,44)*. Other investigators have demonstrated that positive changes in dietary sodium and potassium in the first two decades of life can reduce BP and cardiovascular risk *(35,36,45,46)*. Although the beneficial effects of decreasing sodium intake on BP have been more strongly supported than the effects of increasing potassium intake, few studies have been conducted that evaluate

the influence of potassium on BP levels in youth *(47)*. The purpose of this chapter is to review the nutritional electrolyte-related determinants of BP in children and adolescents, especially focusing on the role of dietary sodium and potassium in regulating casual BP, BP reactivity, and circadian BP patterns in youth.

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 recent national study of 1,658 youth (aged 4–18 years), He and MacGregor *(35)* showed a significant association between sodium intake and systolic BP after adjusting for age, sex, body mass index (BMI), and dietary potassium intake. The magnitude of the association was noted to be similar to that observed in a recent meta-analysis that evaluated the effects of sodium reduction on BP responses in youth *(35)*. In a comprehensive review, Simons-Morton and Obarzanck *(47)* critically evaluated 25 observational studies examining the association between sodium intake and casual BP in children and adolescents: 8 of the papers used self-report measures of dietary intake and 17 papers used urinary sodium excretion. Approximately 67% (two-thirds) of the urinary sodium studies 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 above 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 youth 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 salt sensitive *(48,49)* (i.e., show increased BP in response to high sodium intake). In a study examining the prevalence of salt sensitivity in normotensive African-American adolescents *(50)*, we demonstrated that 22% of healthy normotensive African-American adolescents were characterized as salt sensitive based on definitions established in the adult literature *(51)*. Falkner et al. *(49)* 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 were either salt resistant or had a negative family history of HTN. In a more recent study by Palacios et al. *(52)* African-American girls showed greater sodium retention in response to a low-sodium diet (57 mmol/day) than Caucasian girls, suggesting that sodium handling may contribute to underlying racial differences in susceptibility of developing HTN.

Several investigators have also examined the relationship between salt sensitivity and ambulatory BP profiles in children and adolescents. Wilson et al. examined the relationship between salt sensitivity and ambulatory BP dipping status *(53)*. A significantly greater percentage of salt-sensitive adolescents were classified as nondippers according to mean BP (<10% decrease in BP from awake to asleep) as compared to salt-resistant individuals. Harshfield et al. *(54)* also demonstrated that sodium intake is an important determinant of ambulatory BP profiles in African-American children and adolescents. These findings

are consistent with de la Sierra et al. *(55)* who demonstrated higher awake BP values in normotensive salt-sensitive than in salt-resistant adults.

Rocchini et al. *(56)* conducted a series of studies examining BP sensitivity to sodium intake in obese adolescents. 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 hyperinsulinemia *(56)*. Consequently, sodium retention may be a mechanism underlying the higher concentrations of plasma insulin in obese adolescents. In another study by Lurbe et al. *(57)* 85 obese and 88 nonobese children (aged 3–19 years) participated in 24-h ambulatory BP monitoring and had their urinary sodium excretion rates determined. 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. Obese participants also experienced higher ambulatory BP levels associated with the same levels of sodium excretion than nonobese participants. Taken together, these studies suggest that obesity may be associated with 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 nondipping status in adults *(30,31)*. The role of sodium intake in nocturnal BP has been studied by several investigators. Uzu et al. *(58)* found that nondipper nocturnal BP in salt-sensitive patients was normalized to a dipper pattern (drop from awake to asleep) with sodium restriction. Higashi et al. *(59)* 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.

The mechanism by which sodium sensitivity alters nighttime BP likely involves the sympathetic nervous system. Sympathetic nervous system 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) *(60)*. In a biracial sample of normotensive children, Harshfield et al. *(54)* demonstrated a stronger relationship between sodium handling and casual BP in African-American versus caucasian adolescents. Harshfield et al. *(54)* 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 *(54,60)* and other investigators *(61)* suggest an interactive role for the sympathetic nervous system in sodium retention which may, in part, explain blunted nocturnal decline in ambulatory BP profiles observed in salt-sensitive individuals.

DIETARY POTASSIUM AND BLOOD PRESSURE IN YOUTH

The previously mentioned review by Simons-Morton and Obarzanck *(47)* included 12 observational studies examining 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 only provide partial support for the beneficial effect of high potassium on casual BP levels in youth. However, as Wilson et al. *(33)* have noted 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 Obarzanck's *(47)* extensive review of the literature.

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 *(62)* reported that African-American boys in the highest BP strata, who showed significant increases in BP reactivity, had lower urinary potassium excretion than Caucasians. Among adult populations, Morgan et al. *(63)* demonstrated in hypertensive patients that potassium supplementation (48 mmo1/24 h) prevented the rise in BP produced by postural changes.

Very few reports have characterized the relationship between plasma potassium and ambulatory BP in adults. Goto et al. *(64)* showed a significant negative association between daytime plasma potassium concentration and 24-h systolic and diastolic BP in patients with essential HTN. 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 *(65,66)*. Although there are limitations of plasma potassium values, these results are consistent with prior epidemiological studies, which have shown negative associations between potassium intake, potassium excretion, and BP levels *(67)*.

NUTRITIONAL 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 *(68)*, 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 *(69)*. In another study by Pomeranz et al. *(70)* 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 minerals (32 mg/L) at 6 weeks of age. Among older youth, Cullen et al. *(71)* had 5,881 adolescents and young adults (aged 14–21 years) complete a survey on Youth Risk Behavior. Potassium intake related to fruit consumption declined for males and females during the high school years. Consistent with this finding, Neumark-Sztainer et al. *(72)* 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. Several investigators, including Berenson et al. *(54,73,74)*, have also demonstrated that African-American children and adolescents show lower urinary potassium excretion rates than Caucasians of same age. Thus, targeting adolescents and minority adolescents for dietary interventions that emphasize high-potassium/low-sodium food choices may be particularly needed

at this age 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 (see Table 1). Table 1 provides a summary of the interventions in youth to date 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 and increasing potassium seem to be effective strategies; however, further research is needed to determine the long-term compliance of such interventions in youth.

In a recent meta-analysis by He and MacGregor *(35)* ten 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. *(75)*, the effects of sodium restriction for 12 weeks (60 mEq/24 h) were evaluated on BP responses in Caucasian youth aged 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 *(76,77)*.

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. *(78)* 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. Other researchers have also demonstrated greater reductions to alterations in sodium intake on casual BP responses in African-American children compared to Caucasian children *(79)*.

In their review, Simons-Morton and Obarzanek *(47)* also identified 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. 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 the 11 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. One study that evaluated the effects of increasing potassium was the Dietary Intervention Study in Children (DISC). Participants enrolled in this study had elevated low-density lipoprotein cholesterol. Assessments were done at baseline, 1 year, and 3 years. Longitudinal analyses revealed significant inverse associations between systolic BP and potassium, calcium, magnesium, protein, and fiber and significant inverse associations between diastolic BP and potassium, calcium, magnesium, protein, carbohydrates, and fiber. Direct associations were also found between fat intake and both systolic and diastolic BP. Multivariate models showed calcium, fiber, and fat to be the most important determinants of BP level in children with elevated low-density lipoprotein cholesterol.

Sinaiko et al. *(11)* tested the feasibility of a 3-year potassium supplementation or sodium reduction in preventing the rise in BP among adolescents. Adolescents who were in the upper 15th percentile of BP distribution were randomly assigned to potassium chloride supplementation (l mmol/kg potassium chloride/day), a low-sodium diet (70 mmol sodium/day), or a placebo (normal diet plus placebo capsule). The results demonstrated that both the potassium supplementation and the sodium restriction interventions were effective in reducing the rise of casual BP in girls, but not in boys. The feasibility of long-term restriction of dietary sodium in boys may be limited.

Table 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. (United States) *(103)*	Two group RCT Duration=5 months/group with 8-year 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	*N* = 27 (F = 0 and M = 27) Healthy African-American male infants *Age (months)* = 3 *Race* = 100% African-American *Mean BP* = Not reported	*24-h UNa:* Samples were collected for 3 days via metabolic frames. Na concentration was 11.3 mmol/day in the LS group and 54.8 mmol/day in the CTL group *Food records:* Records showed a reduction in sodium intake consistent with UNa findings	The LS diet did not result in significant changes in BP in the LS group vs. the CTL, at 8-month (88/48 MBP vs. 90/49 MBP) or 8-year follow-up (103/75 MBP vs. 103/76 MBP). BP was significantly correlated with weight but not sodium intake, or sodium or potassium excretion at 8 months
Gillum et al. (United States) *(76)*	Two group RCT Duration=1 year *Family Education Program (FEP; n=41 [children + families])* 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	*N* = 80 children + their families (F = 61% FEP and F = 31% CTL) Children with SBP > 95th percentile for age and sex but SBP < 130 and DBP < 90 mmHg from the Minneapolis, MN public school system	*Food records (3 days):* The FEP group reported significantly lower sodium intake than the CTL group (~25 mmol decrease) *24-h UNa:* Overnight Na excretion did not differ between groups at baseline or 1 year. Poor parent compliance with urine collection method prevented the analyses of parental Na excretion	Based on 3-day 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.

Table 1
(continued)

Authors	*Intervention*	*Sample baseline demographics*	*Compliance*	*Findings*
	Control Group (CTL; n=39) No treatment	*Mean Age (year)* = 7.8 ± 0.7 (FEP); 8.0 ± 0.8 (CTL) *Race* = Not reported *Mean BP* = 111/65 (FEP); 115/69 (CTL)		Urinary sodium excretion did not differ between groups Blood pressure did not differ by group or change over time
Trevisan et al. (United States) *(104)*	Two group RCT Duration=10 weeks/group *Low-Sodium Diet (LS; n=12)* Diet included reduction of sodium intake by ~ 70% *Control Group (CTL; n=9)* Diet similar in composition to LS but without reduced sodium.	*N* = 21 Male and female students from a boarding high school *Age (years)* = 11–15 *Race* = Not reported *Mean SBP* (mmHg)= 108 (LS); 111 (CTL)	*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)

Table 1 (continued)

Authors	*Intervention*	*Sample baseline demographics*	*Compliance*	*Findings*
Hofman et al. (Netherlands) *(105)*	Two group RCT Duration=6 months *Low Sodium Infant Formula (LS; n=225)* Commercially available formula with 33% the concentration of sodium as the control formula. *Control Group (CTL; n=241)* Commercially available formula with sodium included (9.25 mmol/100 kcal) were provided to parents and fed to infants	*N* = 466 (F=49% and M=51%) Newborn infants born within 1 month of each other *Age (week)* = 1 *Race* = Not reported *Mean SBP (mmHg)* = 88 (LS); 87 (CTL)	*Spot UNa:*Na concentration was 22.7 mmol/L in the CTL group and 11.1 mmol/L in the LS group *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 0.89 mol of Na in the LS group	The LS formula group demonstrated a significant decrease in SBP at 25 weeks (–2.00 ±2.13 mmHg)
Cooper et al. (United States) *(106)*	Two group crossover RCT Duration=24-days/condition *Low-Sodium Diet (LS)* Diet included reduction of sodium intake by ~ 200–60 mmol/day via controlled cafeteria meals. Children were instructed not to add salt	*N* = 113 (F=66 and M=47) Adolescent students from a boarding high school without HTN or chronic illness *Mean Age (year)* = 16 *Race* = Not reported *Mean BP (mmHg)* = 109/61	*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 three	Sodium intake was reduced by ~ 58% and SBP and DBP decreased nonsignificantly (–0.6±.70 mmHg; –1.40±1.0 mmHg) following the LS diet

Table 1 (continued)

Authors	*Intervention*	*Sample baseline demographics*	*Compliance*	*Findings*
	or condiments to meals and in-between meal snacks were provided. *Control Group (CTL)* Meals were same as LS group but without reduced sodium		random participants per group per week. Food samples were in close agreement with UNa	Participants with BMI below the median had significant decreases in SBP after the LS diet ($p<0.05$) . Body size may influence BP response to sodium reduction
Calabrese and Tuthill (United States) *(107)*	Two group RCT Duration= 12-weeks/group *Low Sodium Water (LS; n=51)* Bottled water with low sodium (10 mg/L) was provided to children for drinking and family meal preparation and in school classrooms *Control (CTL; n=102)* Bottled water with high sodium (110 mg/L) was provided to children for drinking and family meal preparation and in school classrooms	$N = 153$ (F=75 and M=78) Fourth-grade school children in a community with high sodium in their water distribution system. Children were matched by sex, school, and baseline BP. *Mean Age (year)* = 9 *Race* = Not reported *Mean BP (mmHg)*= 99/58	*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 group. No statistically significant differences were detected between boys and girls	BP levels among girls but not boys in the LS group demonstrated decreased BP over time when compared to the CTL group. Lack of effects for boys may have been due to undetected poorer compliance in boys or other explanations

Table 1 (continued)

Authors	*Intervention*	*Sample baseline demographics*	*Compliance*	*Findings*
Howe et al. (Australia) *(108)*	Two group crossover RCT Duration= 3-weeks/condition *Low Sodium Water (LS)* Parents and children were interviewed by a dietician who provided detailed instruction on adhering to a low-sodium diet *Control Group (CTL)* No treatment	*N* = 21 (F=48% and M=52%) Prehypertensive or hypertensive adolescents *Mean Age (year)* = 11–14 *Race* = Not reported *Mean BP (mmHg)* = *119*/78	*Overnight UNa:* Na/creatinine ratio changed from 179.1 to 101.7 mmol/24 h. *Food Records:* Records showed a reduction in sodium intake consistent with UNa	Overnight UNa demonstrated a reduction in sodium intake of 43.3%. A slight decrease in DBP was demonstrated (–1.3±1.8 mmHg)
Tuthill and Calabrese (United States) *(109)*	Three group RCT Duration= 12-weeks/group *Morning Sodium Capsule (MS)* Participants took one capsule containing 2 g of sodium in the morning and one placebo capsule in the evening each day *Evening Sodium Capsule (ES)* Participants took one capsule containing 2 g of sodium in the evening and one placebo capsule in the morning each day *Placebo Control (CTL)* Participants took two placebo capsules each day	*N* = 216 (F=75 and M=78) Ninth through twelfth grade adolescent girls in a private boarding school. Children were matched by sex, school, and baseline BP. *Mean Age (year)* = 9 *Race* = Not reported *Mean BP* = 99/57 mmHg	*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

Table 1
(continued)

Authors	*Intervention*	*Sample baseline demographics*	*Compliance*	*Findings*
Tochikubo et al. (Japan) *(110)*	Two group RCT Duration=10-weeks/group *Low Sodium Counseling and Self-Monitoring (LS+S; n=12)* Hypertension education and diet counseling including self-monitoring of urinary Cl excretion *Low Sodium Counseling (LS; n=9)* Hypertension education focusing on lowering sodium intake	*N* = 197 (F=17 and M=180) Borderline hypertensive (BHT) and normotensive (NT) students from six high schools in Japan *Age (year)* = 15–18 *Race* = Not reported *Mean SBP (mmHg)* = 150.3±9.8 (BHT); 117.7±12.2 (NT)	*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. Na concentration was significantly higher in the BHT group and K concentration was significantly lower	The LS group did not reduce blood pressure, but sodium excretion (–52 mEq/day), weight (–1.7 kg), and BP (–12/7 mmHg) decreased significantly in the LS+S group. Blood pressure of BHT adolescents may be decreased with dietary education and self-monitoring
Miller et al. (United States) *(75)*	One group CT Duration=12 weeks *Low-Sodium Diet (LS)* Families were instructed to reduce sodium intake to 60 mmol/day to ensure a reduction to 75 mmol/day. Families were instructed to otherwise maintain usual dietary practices	*N* = 149 (F=85 and M=64) Normotensive identical twin pairs, siblings, and parents recruited through a research twin panel and local schools *Mean Age (year)* = 9.7±.4 SEM (F); 10.6 ±.7 SEM (M) *Race* = 100% Caucasian *Mean BP (mmHg)* = 91/54 (F); 95/55 (M)	*Weekly UNa:* Na concentration decreased from baseline to 41.1±1.9 mmol/day (F) and 53.5±3.6 mmol/day (M) at the end of the LS diet	In both sexes there was a significant change in sodium excretion ($p<0.001$) without a change in potassium excretion. For boys there was no change in BP and for girls there was a small but significant decrease in DBP ($p<0.05$). Results suggest that compliance to modest sodium restriction may not consistently lower BP in normotensive children

Table 1
(continued)

Authors	*Intervention*	*Sample baseline demographics*	*Compliance*	*Findings*
Ellison et al. (United States) *(111)*	Two group crossover CT Duration=6 months/conditions *Low- Sodium Diet (LS; 309 students)* Diet included reduction of sodium intake by ~ 15–20% via controlled cafeteria meals and changes in food purchasing and preparation. *Control Group (CTL; 341 students)* Meals were same as LS group but without reduced sodium	*N* = 2 schools (F~51%, M~49%) Male and female students from two boarding high schools in the northeastern United States *Mean Age (year)* = 15 *Race*= ~77% Caucasian *Mean BP (mmHg)* = 107/64	*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, $p<0.01$) and DBP significantly decreased also (–1.5 mmHg, $p < 0.01$)
Myers (Australia) *(112)*	Two group crossover RCT Duration=2 weeks *Low-Sodium Diet (LS)* Participants were advised by a dietician to reduce sodium intake (77±37 mmol/day). Advice was based on previous diet history and 24-h UNa *High-Sodium Diet (HS)* Participants were advised to increase sodium intake (201±37 mmol/day). Advice was based on previous diet history and 24-h UNa	*N*=23 (F=100% and M=0%) Female sodium sensitive (SS) and insensitive (SI) children and adolescents whose parents were affiliated with a hospital in Newcastle, NSW. *Mean Age (year)* = 9 (SS); 12 (SI) *Race* = Not reported *Mean BP (mmHg)*= 108/67	*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 significantly in the LS group (–3.74±2 mmHg; –1.70±2 mmHg

Table 1
(continued)

Authors	*Intervention*	*Sample baseline demographics*	*Compliance*	*Findings*
Nader et al. (United States) *(98)*	Two group RCT Duration=1-year/group *Low-Sodium/Low-Fat diet (LS)* Three months of intensive educational group sessions promoting decreased sodium and fat intake and increased physical activity followed by 9 months of maintenance sessions *Control Group (CTL)* No treatment	$N = 206$ families (623 persons) Mexican-American and Caucasian families recruited through 15 matched elementary schools. Families were defined as one or more children in grades 5 or 6 and one or more adults in the same household *Mean Age (year)* = Not reported *Race* = 26% Caucasian families and 46% Mexican-American families *Mean BP (mmHg)* = Not reported	*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 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
Rocchini et al. (United States) *(78)*	Two group crossover RCT Duration=2-weeks/condition *Low-Sodium Diet (LS)* Participants adhered to a four-day rotating meal plan with meals containing 20–30 mmol/day of sodium	$N = 78$ Obese (n=60) and nonobese (n=18) unmedicated adolescents recruited through pediatricians and school nurses	*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/day)	Obese adolescents had a significantly greater decrease in mean BP when transitioning from a high-sodium diet to a low-sodium diet than nonobese adolescents (–12±1 mmHg vs. +1±2 mmHg; p<0.001)

Table 1
(continued)

Authors	*Intervention*	*Sample baseline demographics*	*Compliance*	*Findings*
	High-Sodium Diet (HS) 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	*Mean Age (year)* = 12.5±.5 SEM (obese); 12.5±.6 SEM (nonobese) *Race* = Not reported *Mean BP(mmHg)* = 125/74 (obese); 106/64 (nonobese)		BP in obese adolescents may be more sensitive to sodium intake
Howe et al. (Australia) *(113)*	Two group crossover RCT Duration=4 weeks/condition *Low-Sodium Diet (LS)* Weekly dietary counseling for both children and parents with low-sodium bread provided *Control Group (CTL)* Weekly dietary counseling for both children and parents with salt sachets provided	*N* = 100 (F=48% and M=52%) School children representing the top, middle, and bottom deciles of the blood pressure range *Age (years)* = 11–14 *Mean BP* = 115/60 mmHg	*First-morning UNa:* Na concentration decreased from 175.9 to 101.8 mmol/day in the LS condition. *Food Records:* A subset of participants completed records and showed a reduction in Na intake consistent with UNa findings	Sodium intake decreased by ∼ 42% in the LS condition and both SBP and DBP declined (–.97±.68 mmHg; –.56±.71 mmHg) though not significantly
Gortmaker et al. (United States) *(100)*	Two group CT Duration=2 years *Eat Well and Keep Moving program (EWKM; n=6 schools)* 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	*N = 14 schools, 479 students* (F= 56% EWKM and F= 61% CTL) Children in grades 4 and 5 from public schools in Baltimore, MD.	Compliance not reported	Based on 24-h recall methods sodium intake did not differ between groups or change over time, though fruit and vegetable intake increased significantly more over time in the EWKM group than the CTL (p=0.01)

Table 1
(continued)

Authors	*Intervention*	*Sample baseline demographics*	*Compliance*	*Findings*
	Control Group (CTL; n=8 schools) No treatment	*Mean Age (years)* = 9.2 (EWKM); 9.1 (CTL) *Race* = 91% African-American *Mean BP (mmHg)* = 115/60		
Wilson and Ampey-Thornhill (United States) *(97)*	One group clinical trial Duration=5 days *Low-Sodium Diet (LS)* Children and families were given guidelines and several food items for maintaining a low-sodium diet	*N* = 184 (F=101 and M=83) Healthy normotensive, unmedicated African-American adolescents recruited from schools, churches, and local recreation centers in the southeastern United States *Mean Age (year)* = 14±1(F); 14±1 (M) *Race* = 100% African-American *Mean BP (mmHg)* = 101/56 (compliant F); 108/53 (compliant M)	*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 Compliant girls reported higher levels of familial dietary support, whereas compliant boys reported lower levels of familial dietary support. Higher dietary support may be associated with adherence in girls

Table 1
(continued)

Authors	*Intervention*	*Sample baseline demographics*	*Compliance*	*Findings*
Pomeranz et al. (Israel) *(70)*	Three group RCT Duration=8-weeks/group *Low Sodium Formula (LS; n=25)* Infant formula diluted with water with 1.4 mmol/L sodium concentration *High Sodium Formula (HS; n=33)* Infant formula diluted with water with 8.5 mmol/L sodium concentration *Control Group (CTL; n=15)* Infants were breastfed	*N* = 58 Newborn Jewish infants in a university-affiliated hospital. Infants from families with history of HTN excluded *Mean Age (week)* = 40±1.3 (LS); 40.2±1.1 (HS); 39.5±1.6 (CTL) *Race* = Not reported *Mean BP (mmHg) = Not reported*	*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 At 24-week follow-up BP values in the LS group increased toward those of the HS group
Palacios et al. (United States) *(52)*	Two group crossover RCT Duration=2-months/condition *Low-Sodium Diet (LS)* 1 g/day, 43 mmol/day of sodium with fixed amounts of dietary potassium. *High-Sodium Diet (HS)* 4 g/day, 174 mmol/day of sodium with fixed amounts of dietary potassium. Packed foods were provided within a 4-day menu cycle and were of the same composition for both groups except for sodium variation	*N* = 36 (F= 100% and M= 0%) Matched African-American (*n*=22) and Caucasian (*n*=14) normotensive adolescent females *Mean Age (years)* = 12.4 (African-American); 13.2 (Caucasian) *Race* = 39% Caucasian and 61% African-American *Mean BP (mmHg)* = 113/59 (African-American); 113/55 (Caucasian)	*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 ($p<0.05$) from baseline to the end of the study. African-American girls showed greater sodium retention in the HS condition than Caucasian girls, though blood pressure did not decrease despite increased sodium retention, nor did sodium excretion increase

Table 1
(continued)

Authors	*Intervention*	*Sample baseline demographics*	*Compliance*	*Findings*
Couch et al. (United States) *(80)*	Two group RCT Intervention=3 months/group *DASH Diet (DASH; n=29)* Initial counseling session with dietician to follow a modified DASH diet. Eight weekly and two biweekly phone calls with interventionists and biweekly mailings *Routine Care(RC; n=28)* Initial counseling session with dietician encouraging consumption of fruits, vegetables, grains, lean meats, and low-fat dairy	*N = 57* (F=21 and M=36) Prehypertensive or hypertensive adolescents seeking treatment in a children's hypertension clinic *Mean Age (years)* = 14.3 ± 2.1 (DASH); 14.4 ± 2.1 (RC) *Race* = 40 Caucasian and 17 African-American *Mean BP (mmHg)* = 131/79 (DASH); 126/82 (RC)	Compliance not reported	The DASH group showed a greater decrease in SBP than the RC (–7.9% vs. –1.5%, p <0.01) There was an increase for DASH participants in fruit servings among DASH participants, with fruit servings increasing ~ 2/day and intake of high-sodium/fat foods decreasing by ~ 0.8 servings/day. Intake of potassium and magnesium reportedly increased by 42 and 36%, respectively

Table 1
(continued)

Authors	*Intervention*	*Sample baseline demographics*	*Compliance*	*Findings*
Potassium interventions				
Wilson et al. (United States) *(32)*	Two group RCT Duration=4-weeks/group *High-Potassium Diet (HK; n=20)* 80 mmol/day 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. *Usual Diet Control (CTL; n=20)* Healthy diet program with weekly 1-h classes covering feedback on food record keeping and 24-h urine results	$N = 40$ (F=18 and M=22) 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) *Mean Age (year)* = 14±1 (dippers); 14±1 (nondippers) *Race* = 100% African-American Mean BP *(mmHg)*= 109±63 mmHg (dippers); 112±61 mmHg (nondippers)	*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 to 114/64), but increased for nondippers (115/62 to 124/67)

Table 1 (continued)

Authors	*Intervention*	*Sample baseline demographics*	*Compliance*	*Findings*
Sorof et al. (United States) *(84)*	Three group crossover RCT; Duration=1-week/condition *Potassium Solution* 1.5 mmol/kg/day *Placebo Solution* Cherry syrup *CVR Stressors* Blood sampling, cold pressor, and video game	*N = 39* (F=33 and M=17) Children aged 7–15 years recruited from schools and clinics with (*n*=22) and without (*n*=17) family history of essential HTN *Mean Age (year)* = 12 *Race*= 44% Caucasian and 56% African-American	*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 Higher vegetable consumption in Caucasian children than in African- American children was associated with higher urinary potassium/creatinine ratio
Wilson et al. (United States) *(33)*	Two group RCT Duration=3-weeks/group *High-Potassium Diet (HK; n=26)* 80 mmol/day 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)* Normal diet program with weekly 1-h classes covering feedback on food record keeping and 24-h urine results	*N* = 53 (F=26 and M=27) Salt-sensitive (SS; *n*=16) and salt resistant (SR; *n*=37) African-American adolescents. Salt sensitivity was defined as an increase in MBP $\geq$ 5 mmHg in transitioning from a low- to high-sodium diet *Mean Age (year)* = 14±1 (SS); 14±1 (SR)	*24-h Urinary potassium:* Dietary K increased significantly over time in the HK group ($p<0.02$) and K levels were significantly higher in the HK group vs. the CTL group	At 3-week assessments all SS participants in the HK group who had been nondippers achieved dipping status due to decreased nighttime DBP Participants in the CTL group did not show decreases in nighttime DBP. Increased potassium intake did not affect weight or sleep duration

Table 1
(continued)

Authors	*Intervention*	*Sample baseline demographics*	*Compliance*	*Findings*
Mu et al. (China) *(114)*	Two group RCT Duration= 2-years/group *Potassium and Calcium Supplementation (KC; n=136)* Children were instructed to take a tablet consisting of 10 mmol potassium and 10 mmol calcium daily *Placebo Control (CTL; n=125)* 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	$N = 261$ (F=133 and M=128) School children in grades 3 and 4 with salt sensitivity (SS) and without salt sensitivity (NSS) from Hanzhong, China *Mean Age (year)* ~ 10.5 *Race* = 100% Asian *Mean BP (mmHg)* = 103/63 (SS/KC); 103/63 (NSS/KC); 103/63 (SS/CTL); 103/63 (NSS/CTL)	*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 significant ($p<0.01$) and was negatively correlated with increase in BP. Moderate increases in dietary calcium and potassium may promote urinary sodium excretion

Table 1
(continued)

Authors	*Intervention*	*Sample baseline demographics*	*Compliance*	*Findings*
Sodium and potassium interventions				
Sinaiko et al. (United States) *(11)*	Three group RCT Duration = 3-years/group *Low-Sodium Diet (LS; n= 70)* 70 mmol/day + nutrition counseling 7 times during months. 1–3 and then tri-monthly. Phone calls were made to reinforce instructions *Potassium Capsule (K; n= 71)* 1 mmol/kg/day, double blind *Placebo Capsule (CTL; n= 69)* Identical to potassium, double blind	*N* = 210 (F=105 and M=105) Minneapolis, MN public school students in grades 5–8 with SBP > 109 mmHg (boys) and 108 mmHg (girls) *Mean Age (year)* = 13.2 ± 0.1 *Race* = 86.5% Caucasian and 13.5% African-American *Mean BP (mmHg)* = 114/63 (LS); 114/67 (K); 114/65 (CTL)	*24-h UNa:* LS group did not achieve 70 mmol/day goal; No change in boys Na excretion (noncompliance); Reduced Na excretion in girls from baseline Percentage of expected capsule use: *Potassium capsule* 84.2%, range=77–93% *Placebo capsule* 91%, range=85–97%	No between-group differences were found for boys and BP increased over time For girls in sodium and potassium interventions BP increased less over time than for placebo groups but did not significantly decrease Differences between boys and girls may be due to poorer compliance in boys Poor compliance in the LS group challenges the feasibility of long-term sodium reduction in adolescents

Table 1
(continued)

Authors	*Intervention*	*Sample baseline demographics*	*Compliance*	*Findings*
Günther et al. (United States) *(81)*	Cross-sectional study *Type 1 diabetes (T1D; n= 2440)* *Type 2 diabetes (T2D; n= 390)* All participants' diets were analyzed and assessed for concurrence with eight food groups of the Dietary Approaches to Stop Hypertension (DASH) diet for increased fruit and vegetable intake	*N* = 2830 (F=54% and M=46%) Participants in the SEARCH for Diabetes in Youth trial aged 10–22 with type 1 or type 2 diabetes *Mean Age (year)* = 14.7–16.6 *Race T1D* = >71% Caucasian, >5% African-American, and >11% Hispanic *Race T2D* = >20% Caucasian, >30% African-American, >14% Hispanic, and >12% Native American *Mean BP (mmHg)* = 108/68	Participants' diets were analyzed using a self-report Food Frequency Questionnaire from which a DASH concurrence score was calculated	In youth with T1D adherence to DASH was inversely associated with HTN, where as in youth with T2D adherence to the DASH diet was not associated with reductions in the risk of HTN

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.

In a study by Couch et al. *(80)*, the DASH diet 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 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 *(81)* 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. Note, however, that in the Günther et al. *(81)* 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 *(82)* have conducted a number of investigations evaluating how altering dietary sodium affects CVR. 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 essential HTN showed an increase in resting baseline and stress BP levels and the girls with a negative family history did not. These findings have been replicated in young adults *(83)*. However, for those with a positive family history of essential HTN, changes from baseline to stress were similar before and after salt loading.

Sorof et al. *(84)* examined whether CVR was inversely related to the dietary intake of potassium in 39 children. 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/day 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 *(84)*, Wilson et al. *(33)* demonstrated no significant change in BP reactivity in African-American adolescents who complied with a 3-week high-potassium diet. Wilson et al. *(33)* also demonstrated, in a randomized control trial among adolescents, that increasing potassium was beneficial for reversing nondipping status and elevated nighttime BP in African-American adolescents. This study examined the effects of increasing dietary potassium on BP nondipping status in salt-sensitive and salt-resistant African-American adolescents. Urinary potassium excretion significantly increased in the treatment group (35 ± 7 to 57 ± 21 mmol/24 h). At baseline, a significantly greater percentage of salt-sensitive (44%) subjects were nondippers 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 exists, although daytime BP may be unchanged by a high-potassium diet. Our data are the first to indicate that increasing dietary potassium reversed nondipping 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 *(85)* 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 nonsupplemented hypertensive patients. Svetkey et al. *(86)* 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.

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 *(12,67,87)*. The mechanisms underlying BP nondipping status are unknown. One potential mechanism by which potassium may alter nighttime BP may involve potassium-related natriuresis *(88,89)*. Restricting potassium intake leads to sodium retention; potassium supplementation results in a 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 *(67)*. If nondippers are characterized by elevated sympathetic nervous system activity and increased peripheral resistance during sleep, this potassium-mediated vasodilatory effect could explain the reversal of nondipping status in the Wilson et al. study *(33)*. Other studies that support this hypothesis show that intrabrachial arterial infusions of potassium chloride increase forearm blood flow and decrease forearm vascular resistance in healthy adults *(90,91)*. Potassium supplementation given in combination with a high-sodium diet also suppresses the increase in catecholamine responses typically seen in response to salt loading *(92)*. Previous studies have shown that total peripheral resistance and norepinephrine responses to stress are greater in offspring of hypertensives than in normotensives *(93)*. Several adult studies have also confirmed that sympathetic nervous system activation occurs in individuals with elevated nighttime BP *(94)*. Taken together, these data support the hypothesis that the sympathetic nervous system may have a controlling influence on nondipping 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 *(95)*. 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 *(96)*.

Social support from family members may be one way that parental involvement may 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 *(97)* examined the relationship between gender, dietary social support (emotional), and compliance to a low-sodium diet. A total of 184 healthy African-American adolescents 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 a study by Nader et al. *(98)*, Caucasian, African-American, and Mexican-American families were randomly assigned to a 3-month low-sodium, low-fat dietary program, or to a no-treatment group. The treatment group showed a greater increase in social support specific to diet than the no-treatment group. Taken together, these studies provide evidence that familial support may be important for increasing adolescents' compliance with healthy dietary programs that will 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 et al. *(99)* randomly assigned adolescents to peer-led or teacher-led promotions of a low-sodium, low-fat dietary intervention. At the end of the intervention, both groups showed equal effectiveness in changing nutritional habits. The peer-led group, 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. *(100)* 1,295 sixth- and seventh-grade students from public schools in Massachusetts participated in a school-based intervention over 2 years to reduce the prevalence of obesity. The intervention was based on social cognitive theory (SCT) and behavioral choice theory. Treatment sessions were incorporated into the existing curricula, used classroom teachers, and targeted 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, the intervention school children 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 *(101)*. 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 fruits in all meals may be one effective approach to improving electrolyte intake in children. Further research is needed, specifically more tests that systematically focus on the relevance of increasing fruit and vegetable intake throughout an entire day's eating episodes instead of sporadically.

Several studies have demonstrated sex differences in compliance to sodium restriction and dietary potassium supplementation. Sinaiko et al. *(11)* reported urinary electrolyte excretion data over the course of a 3-year intervention in fifth through eighth graders. Boys were less likely to comply with a sodium restriction of 70 mmol/day than girls. Subsequently, BP effects were only significant for girls. In a study by Wilson and Bayer *(102)*, boys were more likely than girls to comply with a 3-week dietary intervention of increasing potassium to 80 mmol/day 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 vs. 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 nondipping ambulatory BP 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.

Reducing sodium and increasing potassium intake have been shown to be 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 with high-potassium dietary interventions may be easier than with 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, including African-Americans, are at particularly high risk for developing HTN in early adulthood, and efforts should focus on preventing HTN in these and underserved communities. Continued efforts will be needed to assure prevention of obesity in underserved and minority youth. Abnormal sympathetic nervous system 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 sympathetic nervous system activation. The precise physiological mechanisms that underlie the observations reported in this chapter should be another focus of future investigations.

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16 Ethnic Differences in Childhood Blood Pressure

Gregory A. Harshfield, PhD

Contents

ETHNIC DIFFERENCES IN HYPERTENSION, MORBIDITY, AND MORTALITY

Ethnic differences in essential hypertension (EH) and blood pressure-related morbidity and mortality are well established. According to the 2009 report from the American Heart Association *(1)*, the prevalence of essential hypertension in blacks in the United States is among the highest in the world and continues to increase. From 1988–1994 to 1999–2002, the prevalence of EH in black adults increased by 5.6% (35.8–41.4%), and it was particularly high among black women at 44.0%. In contrast, the prevalence among white adults increased by only 1.8% (24.3–28.1%) *(2)*. Hypertension in blacks contributed to a 1.3 times greater rate of nonfatal stroke, a 1.8 times greater rate of fatal stroke, a 1.5 times greater rate of heart disease death, and a 4.2 times greater rate of end-stage kidney disease *(1)*.

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_16
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DO ETHNIC DIFFERENCES IN BLOOD PRESSURE BEGIN IN YOUTH?

It is not clear when ethnic differences in blood pressure (BP) or EH become apparent. In the most recent edition of the *Hypertension Primer*, Morgenstern and Sinaiko *(3)* state "No significant differences have been found in blood pressure until adolescence." However, we identified in 56 studies that reported data for casual BP on black and white youth. Of these, 33 (62%) reported higher BPs for blacks, 10 (18%) reported higher BPs for whites, and 13 (23%) reported no differences. In 1993 Alpert and Fox *(4)* reviewed and performed a meta-analyses in which they observed that blacks had higher BP in 50% (19/38) of the comparisons for subjects 0–12 years, 66% (33/50) of the comparisons for subjects 13–18 years, 80% (4/5) of the comparisons for 19–24 years, and 100% (10/10) of the comparisons across the multiple age range. Overall, these data suggest that ethnic differences may not become apparent until an older age. Consistent with this hypothesis are the results of a study by Manatunga et al. *(5)* that examined ethnic differences in a prospective longitudinal assessment of BP in 345 white children and 164 black children. Each child had their BP measured every 6 months for 2–5.5 years. The mean BP and the mean rate of increase in BP over time were compared between gender-specific black and white groups. For both boys and girls, the mean systolic BP was 2 mmHg higher in black children than white children and the mean diastolic BP was 1.5 mmHg higher in black children than in white children. More importantly, the rate of increase in BP over time was significantly greater in blacks than whites. Voors et al. *(6)* reported on data from the Bogalusa Heart study. Black children had significantly higher BP than white children. This difference, starting before age 10, was largest in the children in the upper 5% of the BP ranks. Daniels et al. *(7)* evaluated ethnic differences in BP in girls aged 9–10 years in the National Heart, Lung, and Blood Institute Growth and Health Study (NGHS) and the extent to which these differences were explained by sexual maturation and body size. The NGHS enrolled 539 black and 616 white girls aged 9 years and 674 black and 550 white girls aged 10 years. The black girls compared to white girls had significantly higher systolic and diastolic BP (102/58 vs 100/56 mmHg). The stage of maturation was found to account for the difference. Daniels concluded that the effect of sexual maturation on BP appears to operate through height and body fat and that the effect of obesity may be more important for systolic BP than diastolic BP. Another study by Daniels et al. *(8)* assessed the longitudinal changes in BP in black and white adolescent girls and evaluated potential determinants of changes in BP, again including sexual maturation and body size. A total of 1213 black and 1166 white girls, aged 9 or 10 years at study entry, were followed up through age 14 with annual measurements of height, weight, skinfold thickness, stage of sexual maturation, BP, and other cardiovascular risk factors. Average BPs in black girls were generally 1–2 mmHg higher than in white girls of similar age over the course of the study. Age, race, stage of sexual maturation, height, and body mass index (kg/m^2) were all significant predictors of systolic BP and diastolic BP in longitudinal regression analyses. They observed that ethnic differences in BP were seen at all stages of maturation indicating additional factors are also important. Body mass index (BMI) had a lesser impact on BP in black girls; however, BMI increased at a greater rate with age in black girls which may have contributed to the ethnic differences in BP. Overall, in their study at higher BMIs there are no ethnic differences in BP; however, at lower BMIs black girls had higher BPs, which were not accounted for by maturation differences. Between ages 9 and 14, BMI increased with age at a greater rate in black girls, which helped account for the maintenance of ethnic differences in BP between ages 9 and 14. Liebman et al. *(9)* assessed BP levels, anthropometric parameters, and dietary intakes

in 1981 and 1983 in a population of black ($n = 236$) and white ($n = 296$) adolescent girls aged 14 and 16 years in 1983. The 14-year-old black girls exhibited significantly higher mean SBP and DBPs than whites in both years. Body weight and Quetelet index were more strongly associated with BP than were height and triceps skinfold thickness. Rabinowitz et al. *(10)* assessed differences in the prevalence of BP ≥95th% (i.e., EH on an initial screening of 3349 students by race, sex, and age. The overall prevalence of EH in this urban adolescent population was 8.1%. Significant ethnic differences were present in females (blacks = 6.6% vs non-Hispanics = 2.9%, $p < 0.01$). Within the black females, EH occurred more frequently among the girls attending predominantly black public schools (7.7%) compared to an interracial parochial school (2.0%), $p < 0.001$. This difference could not be explained by weight, height, or the occurrence of obesity. However, the prevalence of obesity was higher in the adolescents with EH and among females with EH. Obesity was also present in a greater number of blacks than whites. The observed BP differences within black females, by school, may reflect a family–environment effect on cardiovascular risk.

In contrast to the studies cited above, other studies have not observed ethnic differences in BP. Rosner et al. *(11)* analyzed BPs from eight large epidemiologic studies published between 1978 and 1991 that included measurements of 47,196 children on 68,556 occasions for systolic BP and of 38,184 children on 52,053 occasions for diastolic BP. They conclude that "there are few substantive ethnic differences in either SBP or DBP during childhood and adolescence. The differences that were observed were small, inconsistent, and often explained by differences in body size." A longitudinal study by Baron et al. *(12)* did not find " substantial" ethnic differences in BPs between blacks, whites, and Mexican Americans prior to 20 years of age. Morrison et al. *(13)* also did not find ethnic differences in a biracial group of 682 schoolchildren, aged 6 through 19. Hohn et al. *(14)* assessed racial differences in BP levels in youth of Asian, black, Hispanic, and non-Hispanic white descent. They obtained BP measurements from 4577 ninth grade students during the spring of the years 1985–1989 (39% black, 30% Hispanic, 21% white, 10% Asian; 50% female) with a mean age of 15 years. They found no differences between black and white youth.

ETHNIC DIFFERENCES IN AMBULATORY BLOOD PRESSURE MONITORING

Ambulatory BP monitoring (ABPM) has become the standard for many physicians and scientists for the identification of individuals with EH and to assess the effectiveness of treatment *(12,15–21)*. ABPM has been proven to be superior to casual BP for the prediction of cardiovascular morbidity and mortality *(22–29)*. The use of ABPM is also recommended for use in children and adolescents *(30)* in whom it has been proven to be cost effective *(31)*.

In 1987, we presented data at the Interdisciplinary Conference On Hypertension in Blacks *(32)* from 35 black adults that showed a blunted nocturnal decline in BP, now referred to as non-dipping. Specifically, the subjects only showed about a 10% drop in BP from daytime to nighttime compared to a 15% drop which we had previously observed in white patients. This was the first report to our knowledge of this pattern in a healthy population. This ethnic difference has now been reported in a multitude of studies by many groups and is a well-established finding (for reviews, see *(33–35)*). Several studies demonstrated the clinical significance of the blunted nocturnal decline in BP in blacks. Fumo et al. *(36)* were the first to report that the pattern was associated with target organ changes to the heart, a finding confirmed by Mayet et al. *(37)* and Olutade et al. *(38)*. We demonstrated

that the blunted nocturnal decline in black adolescents is associated with decreased renal function *(39)*. We also reported that the ethnic difference in ABPM is already apparent during adolescence *(40–43)*. Most recently, Wang et al. *(44)* of our group reported data for race differences in ABPM derived from a longitudinal study conducted at the GPI. Recordings were measured up to 12 times over 15 years for 312 black and 351 white subjects. We found significant ethnic differences in longitudinal trajectories. Black males had higher levels than white males and females, and black males and females showed a faster increase of BP with age, with greater differences in nighttime systolic BP than daytime BP.

Further studies identified factors related to the difference. Two of these factors, fitness *(45)* and body size *(46)*, are clearly related. Both decreased fitness level and increased body size had a greater effect on nighttime BP of African-Americans than Caucasians. The third factor was sodium intake *(47)*. We observed that sodium intake as determined by excretion was related to daytime and nighttime BP in African-Americans but not Caucasians. These findings are consistent with the well-known differences in the influence of sodium intake on casual BP (for recent reviews, see *(48–51)*). Further studies demonstrated that the differences in patterns are stable over time *(42,44)*.

ETHNIC DIFFERENCES IN BP-RELATED TARGET ORGAN DAMAGE IN YOUTH

Some studies suggest that black adolescents are characterized by greater BP-related target organ damage, although these findings are not universal. Burke et al. *(52)* using data from the Bogalusa Heart study did not observe ethnic differences for subjects aged 7–22. Daniels et al. *(53,54)* reported similar findings. Schieken et al. *(55)* reported data on twins aged 11–17 across 5 years. Blacks had greater left ventricular mass in visit that was not sustained across the visits. In contrast, we reported *(42)* greater LV mass in blacks with a mean age of 13 years which was associated with higher nighttime BP. Consistent with these results, Dekkers et al. *(56)* reported that ethnic differences in LV mass were expressed in early adolescence, and they persisted when controlling for socioeconomic status and anthropometric and hemodynamic variables. In another study, Kapuku et al. *(57)* reported data on a sample of 147 subjects aged 1–19 years tested on two occasions. Blacks compared to whites had greater relative wall thickness and left ventricular mass coupled with lower midwall fractional shortening ratio on both occasions.

We have also reported greater BP-related target organ damage to the kidney in black adolescents *(58)*. Specifically, in a sample of 317 adolescents, the blacks compared to whites had an approximately 10% greater rate of excretion of microalbumin. This pattern was in turn associated with impaired sodium regulation.

MECHANISMS UNDERLYING ETHIC DIFFERENCES IN BLOOD PRESSURE IN YOUTH

Many factors have been hypothesized to account for ethnic differences in BP and ABPM. These include genetic factors that control BP regulatory systems including the renin–angiotensin–aldosterone system, the sympathetic nervous system, the endothelial system, and inflammatory responses. We have been examining factors related to differences in BP regulation and the development of BP-related target organ damage within the Black pediatric population. Impaired sodium regulation is hypothesized to underlie the

development and maintenance of EH in a significant percent of the hypertensive population. This is particularly true for high-risk populations that are characterized by a volume-dependent form of EH, including blacks and obese individuals (for recent reviews, see *(48–51)*). The hypothesis is based on the premise that BP is to maintain sodium homeostasis or sodium balance. This is accomplished by what is referred to as the renal-body fluid system *(59)*. The system operates as follows: a fall in BP such as would occur with severe hemorrhage increases the kidney's reabsorption of both water and sodium. This increases intracellular fluid volume, blood volume, and cardiac output to maintain BP and blood flow to the brain. Alternatively, an increase in BP increases the kidney's excretion of water (pressure diuresis) and sodium (pressure natriuresis), leading to a decrease in intracellular fluid volume and blood volume. This reduces cardiac output, which lowers BP. In normal individuals sodium homeostasis is maintained across a wide range of sodium intakes. In contrast, a higher level of BP is required to maintain sodium balance at high salt intake in individuals with a reduced ability to excrete sodium.

Blacks have a greater prevalence of stress-induced sodium retention. Light and Turner *(60)* examined 28 adults which included 14 blacks and 14 whites. The blacks had lower sodium excretion during a 1-h stress period, with a reduction in sodium excretion for 6 of the 14 black and 2 of the 14 white subjects. We *(61)* next reported race differences in stress-induced sodium retention using a protocol that examined concurrent changes in BP and sodium excretion across a series of tasks (playing video games, ice to forehead) in black and white youths with a positive family history of EH. The blacks had a greater increase in BP coupled with a smaller increase in sodium excretion averaged across the tasks. A second study *(62)* by our group tested 118 black youth. Of these, 38 (32%) retained sodium during stress. Sodium retention resulted in a cardiac output-related increase in BP across the stress period. This contrasted with the subjects that showed the expected increase in sodium during stress period was related to total peripheral resistance. Significantly, sodium retention resulted in a delay in the return of BP to pre-stress levels. This would be expected with the volume-mediated increase in BP which remains elevated until the volume expansion diminishes. As such, these individuals were exposed to a greater BP load than those individuals with the normal pressure natriuresis response. The third study by our group examined the interaction between race and sex on stress-induced sodium retention *(63)*. The 190 subjects included 94 boys (41 black, 53 white) and 96 girls (44 black, 52 white). Whites compared to blacks had a greater change in sodium excretion, as did boys compared to girls. The race by sex interaction was significant for the change in systolic BP, with white girls showing a smaller change than the other three race/sex groups.

Stress-induced sodium retention has also been demonstrated in animal models of EH. The initial report by Friedman and Iwai *(64)* was published in *Science* in 1976. They demonstrated that behavioral stress hastened the development of EH in Dahl salt-sensitive rats, a strain genetically predisposed to develop salt-sensitive EH. Koepke and his colleagues *(65,66)* performed a comprehensive series of studies on stress-induced sodium retention. They were among the first to describe stress-induced sodium retention in the spontaneously hypertensive rat model. They also demonstrated that high dietary sodium intake augmented the responses and that renal denervation corrected the impairment independent of sodium intake. Further studies localized two areas of the brain which contribute to this response pattern. Both of these areas are known to be involved in the perception of stress. Specifically, injection of a beta-2 receptor antagonist into the posterior hypothalamus or an alpha-2 receptor agonist into the amagdaloid nucleus abolished the renal responses. A subsequent study and more recent studies by others *(67–69)* suggest that the anti-natriuretic

actions of stress-induced efferent renal sympathetic activity are the result of both direct actions on the kidney and resultant increases in angiotensin II. Lawler and Cox *(70)* developed an animal model of EH which they called the borderline hypertensive rat. The strain is normotensive unless it is exposed to either chronic stress or a high-sodium diet. Furthermore, stress-induced EH is associated with suppressed plasma renin activity, implicating impaired regulation of the renin–angiotensin–aldosterone system *(71)*. Of particular interest for the current study was the finding that this strain showed delayed recovery from an aversive conditioning task *(72)*. DiBona utilized the borderline hypertensive rat strain to examine the impact of stress on the development of EH. These studies confirmed previous results that demonstrated that the stress-induced sodium retention was the result of an increase in efferent renal sympathetic nerve activity *(73–77)*. A series of studies by Anderson et al. *(78–81)* examined the relationship between stress and sodium regulation in dogs. Their basic protocol was to expose two groups of dogs to avoidance conditioning training for 30 min a day for 15 days. One group was on a normal diet, and a second group received a constant rate of infusion of 185 mEq of sodium. The sodium-loaded dogs had a rapid development of EH. The EH was associated with immediate and sustained reductions in sodium excretion.

SUMMARY AND CONCLUSION

Overall, the studies suggest that black adolescents have higher levels of BP than their white counterparts. Furthermore, the differences are related to the premature development of BP-related target organ damage to the heart, vasculature, and kidneys. Of interest has been the research on the physiological mechanisms underlying differences within the black population. These data suggest significant heterogeneity in the mechanisms underlying BP regulation which is important for the treatment of hypertension in this population.

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17 Childhood Obesity and Blood Pressure Regulation

Albert P. Rocchini, MD

Contents

INTRODUCTION

Childhood obesity is the most common nutritional problem in children from both developed and non-developed countries. From the 1960s to 1990s, the prevalence of obesity in children grew from 5 to 11% *(1)*. In adults, obesity is recognized as an independent risk factor for the development of both hypertension and cardiovascular disease. In childhood there are data to demonstrate a strong relationship between childhood obesity and hypertension, type 2 diabetes mellitus, dyslipidemia, obstructive sleep apnea, left ventricular hypertrophy, and orthopedic problems. This chapter will summarize (1) the epidemiologic evidence that substantiates obesity as an independent risk factor for the development of hypertension in

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_17
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both adults and children; (2) an explanation of how obesity may cause hypertension; (3) a brief summary of other cardiovascular abnormalities associated with obesity; and (4) a brief summary of how to manage the hypertensive obese child.

RELATIONSHIP BETWEEN OBESITY AND HIGH BLOOD PRESSURE

Epidemiological Studies Linking Obesity to Hypertension

The association between obesity and hypertension has been recognized since the early 1900s. Several large epidemiological studies documented the association between increasing body weight and an increase in blood pressure *(2–13)*. For example, Symonds *(4)* analyzed 150,419 policyholders in the Mutual Life Insurance Corporation and documented that systolic and diastolic blood pressure increased with both age and weight. The Framingham study *(5)* documented that the prevalence of hypertension in obese individuals was twice that of those individuals who were normal weight. This relationship held up in all age groups of both women and men.

The association of obesity and hypertension in children has also been well documented. Rosner and co-workers *(14)* pooled data from eight large US epidemiological studies involving over 47,000 children. Irrespective of race, gender, and age, the risk of elevated blood pressure was significantly higher for children in the upper compared to the lower decile of body mass index. Freedman et al. *(15)* reported that overweight children were 4.5–2.4 times as likely to have elevated systolic and diastolic blood pressure. Similarly, Sorof et al. *(16)* reported a three times greater prevalence of hypertension in obese compared to non-obese adolescents in a school-based hypertension and obesity screening study. Thus, a large number of population-based studies have documented a strong association between obesity and hypertension in both sexes, in all age groups and for virtually every geographical and ethnic groups.

Relationship of Weight Gain to Blood Pressure Level

There have been no studies in humans that have investigated the effect of weight gain on blood pressure. However, in the dog, it has been shown that weight gain is directly related to an increase in blood pressure. Cash and Wood in 1938 *(17)* demonstrated that weight gain caused dogs with renal vascular hypertension to further increase their blood pressure. Rocchini et al. *(18,19)* and Hall et al. *(20)* found that normal mongrel dogs fed a high-fat diet gained weight and developed hypertension. In these dogs the hypertension was associated with sodium retention, hyperinsulinemia, and activation of the sympathetic nervous system.

Effect of Weight Loss on Blood Pressure Level

Weight loss is associated with a lowering of blood pressure. Haynes *(21)* reviewed the literature up to the mid-1980s on the relationship of weight loss to reductions in arterial pressure. He used strict criteria to examine only well-done studies and noted that there were only six studies available. Three of the six studies that meet Haynes criteria demonstrated a clear effect of weight loss on lowering arterial pressure. Many clinical trials published since the late 1970s have clearly documented the blood pressure lowering effect of weight loss *(21–35)*. For example, the Hypertension Prevention Trial *(23)* documented that in individuals with borderline elevations in blood pressure a mean weight loss of 5 kg was associated with as much as a 5/3 mmHg decrease in blood pressure. Thus, based on numerous weight

loss studies, calorie restriction and weight loss are associated with a reduction in blood pressure. In addition, it is clear that even modest weight loss (i.e., 10% loss of body weight) improves blood pressure, and many individuals achieve normal blood pressure levels without attaining their calculated ideal weight.

A limitation with the use of studies documenting that weight loss is associated with a reduction in blood pressure is that most studies do not address the long-term effect of weight change on blood pressure in subjects who are again placed on unrestricted diets. Dornfield and co-workers *(34)* reported that over a follow-up of 1–4 years after weight loss, changes in blood pressure still correlated with changes in body weight. However, recent data suggest that long-term weight loss may not reduce the incidence of hypertension. Sjöström et al. *(36)* compared the incidence of hypertension and diabetes in 346 patients undergoing gastric surgery with 346 obese control subjects who were matched on 18 variables. After 8 years, the surgical group had maintained a 16% weight loss, whereas the control subjects had a 1% weight gain. These investigators demonstrated that weight reduction in the surgical group had a dramatic effect on the 8-year incidence of diabetes, but had no effect on the 8-year incidence of hypertension. They *(37)* and others *(38)* previously documented that surgical weight loss positively affected blood pressure at 2 and 4 years of follow-up, but that this effect on blood pressure is lost after 8 years of follow-up. These authors have speculated "that remaining obesity in the surgically treated patients could have induced a reappearance of hypertension during the course of the study independent of ongoing weight maintenance." Therefore, Sjöström's study suggests that a relapse of hypertension after surgically induced weight loss does occur despite the maintenance of significant long-term weight loss and that the pathogenesis of recurrent hypertension is not well understood *(39)*.

Effect of Body Fat Distribution on Blood Pressure

The definition of obesity also contributes to the controversy regarding the independence of obesity as an etiological determinant of hypertension. Obesity is defined not just as an increase in body weight but rather as an increase in adipose tissue mass. Adipose tissue mass can be estimated by multiple techniques such as skinfold thickness, body mass index ([weight in kg]/[height in meters]^2), hydrostatic weighing, bioelectrical impedance, water dilution methods, computed tomography, and magnetic resonance imaging (MRI). In most clinical studies, body mass index is usually used as the index of adiposity. Obesity is generally defined as a body mass index of greater than 30 kg/m^2 in adults and >95th percentile for children and adolescents. In 1956, Jean Vague *(40)* reported that the cardiovascular and metabolic consequences of obesity were greatest in individuals whose fat distribution pattern favored the upper body segments. Since that observation, several population-based studies have demonstrated that upper body obesity is a more important cardiovascular risk factor than body mass index alone *(41–47)*. These studies suggest that increased visceral adipose tissue (VAT) as opposed to subcutaneous adipose tissue (SAT) relates better to the development of systemic hypertension. For example, the Normative Aging Study *(41)* has demonstrated that there is a significant relationship between abdominal circumference and diastolic blood pressure. In fact, the risk of developing hypertension was better predicted by upper body fat distribution than by either body weight or body mass index. Similarly, Fox et al. *(48)* demonstrated in 3001 participants from the Framingham Heart study that although both SAT and VAT are associated with the prevalence of hypertension, only VAT provides significant information above and beyond percent fat and waist circumference. In both children and young adults, Shear et al. *(42)* reported that blood pressure correlated

strongly with upper body fat pattern, but not with measures of global obesity. Many investigators have demonstrated that the association of obesity to increased cardiovascular risk is primarily related to upper body adiposity *(49,50)*. There is limited information relating fat distribution to blood pressure in the pediatric population.

Finally, in dogs that develop hypertension by being fed a high-fat diet, they increase their abdominal circumference significantly more than their thoracic circumference *(51)*. MRI studies in fat-fed dogs also demonstrate a marked increase in omental and subcutaneous fat *(52)*. We also have preliminary data in dogs fed a high-fat diet that demonstrates a stronger relationship between the increase in blood pressure and the increase in abdominal circumference as compared to the increase in total body weight (Fig. 1).

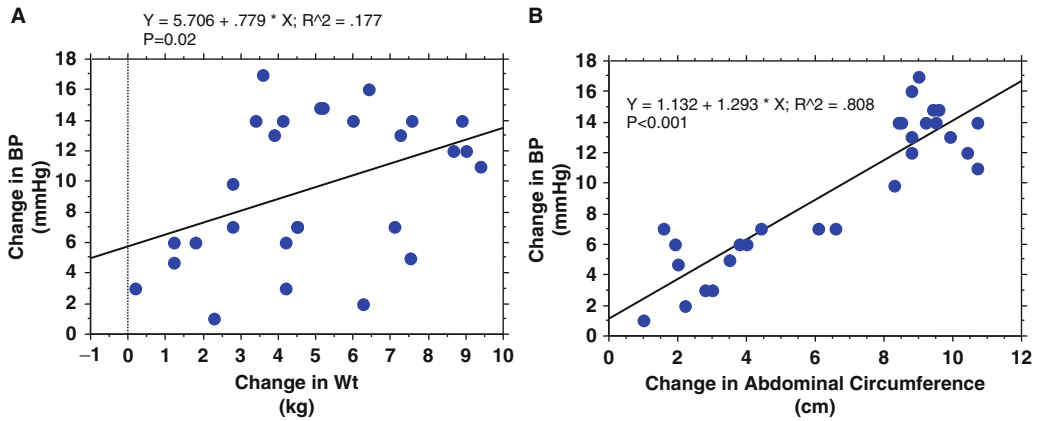

Fig. 1. The relationship between change in blood pressure and change in total body weight (panel A) or abdominal circumference (panel B) in seven dogs who received a high-fat diet for 5 weeks is depicted. Although blood pressure significantly correlates to the change in total body weight that the dogs experience when receiving the high-fat diet, the change in abdominal circumference is responsible significantly more of the variance in blood pressure.

Summary

We know that obesity is directly related to hypertension based on strong epidemiologic data, animal studies which demonstrate that weight gain causes hypertension, and many human studies which demonstrate that weight loss results in a reduction in blood pressure. In addition, it appears that it is abdominal adiposity, rather than general adiposity that is primarily related not only to the hypertension but also to the increased cardiovascular risk associated with being obese.

MECHANISM(S) WHEREBY OBESITY MIGHT CAUSE HYPERTENSION

The exact pathophysiologic mechanism whereby obesity causes hypertension is still unknown. Obesity hypertension is complex and multifactorial. It is clear that obesity hypertension directly relates to abnormal renal sodium handling and that this alteration in sodium handling is predominately mediated through activation of the sympathetic nervous system and to a lesser extent through activation of the renin–angiotensin–aldosterone system. However, what is less clear is how obesity initiates the activation of the sympathetic nervous system (Fig. 2).

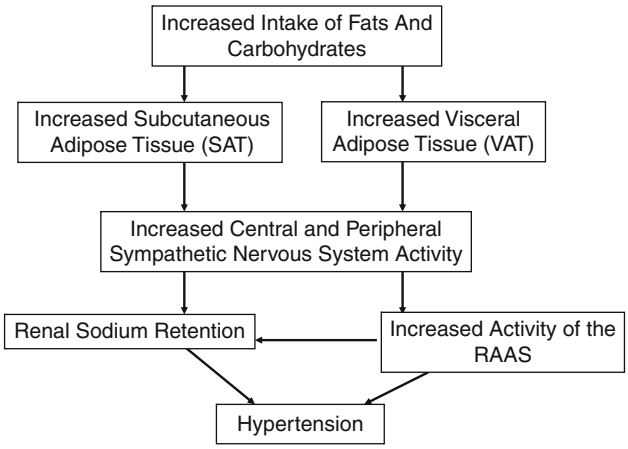

Fig. 2. A schematic representation for how the development of obesity might result in hypertension. SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; RAAS, rennin–angiotensin–aldosterone system.

Abnormal Renal Sodium Handling and Obesity Hypertension

Most investigators believe that fluid retention is the final common pathway that links obesity to hypertension. There is ample human and animal data linking obesity hypertension to fluid retention. Rocchini et al. *(33)* demonstrated that prior to weight loss, the blood pressure of a group of obese adolescents was very sensitive to dietary sodium intake; however, after weight loss, the obese adolescents lost their blood pressure sensitivity to sodium. These investigators demonstrated that when compared to non-obese adolescents, the obese adolescents have a renal-function relation (plot of urinary sodium excretion as a function of arterial pressure) that has a shallower slope. They demonstrated that the renal-function relationship is normalized by weight loss (Fig. 3).

There are also animal data that suggest that sodium retention is associated with obesity hypertension. In a dog model of obesity-induced hypertension, Rocchini et al. *(19)* demonstrated that during the first week of the high-fat diet, the increase in sodium retention appeared to best relate to an increase in plasma norepinephrine activity; whereas, during the latter weeks of the high-fat diet, an increase in plasma insulin appeared to be the best predictor of sodium retention. Rocchini also demonstrated that the hypertension associated with weight gain in the dog occurs only if adequate salt is present in the diet. Hall and co-workers *(53)* demonstrated that obesity-induced hypertension in the dog is associated with increased renal tubular sodium reabsorption since marked sodium retention occurred despite large increases in glomerular filtration and renal plasma flow. Granger et al. *(54)* demonstrated that dogs fed a high-fat diet develop an abnormal renal pressure–natriuresis relationship similar to that observed in obese adolescents.

The relationship between urinary sodium excretion and mean arterial pressure can be altered by intrinsic and extrinsic factors that are known to affect the ability of the kidney to excrete sodium (Table 1). Although both obese humans and animals can have compression of the kidney by the surrounding fat and that fat may penetrate the renal hilum into the sinuses surrounding the renal medulla *(55,56)*, it is unlikely that a fat-based structural change in the kidney is the major pathophysiological cause of the renal sodium retention associated with obesity. Based on both human and animal data, insulin resistance, activation

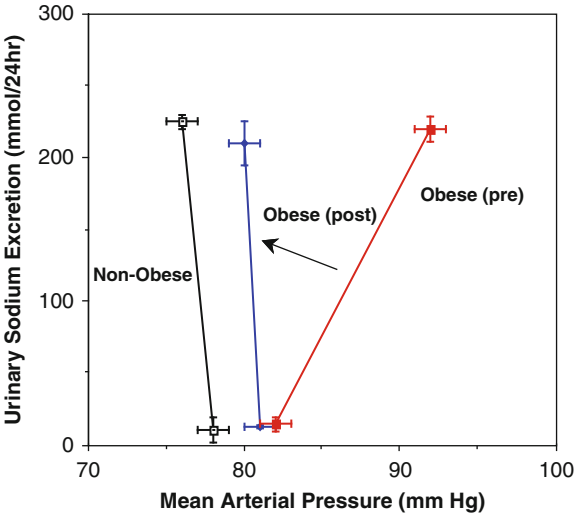

Fig. 3. Renal-function relations for 18 non-obese (X) and 60 obese adolescents before a weight loss program (*open square*) and the 36 obese adolescents who lost weight during a 20-week weight loss program (*closed square*). In comparison with the non-obese adolescents' renal-function relation, the obese adolescents' renal-function relation has a shallow slope ($p<0.001$). In those who lost weight, the slope increased (*arrow*). This increase was due to a decrease in the mean arterial pressure during the 2 weeks of the high-salt diet. From *(33)*.

Table 1
Factors That Produce Alterations in the Renal-Function Curves

1.	Constriction of the renal arteries and arterioles
2.	Changes in glomerular filtration coefficients
3.	Changes in the rate of tubular reabsorption
4.	Reduced renal mass
5.	Changing levels of renin–angiotensin activation
6.	Changing levels of aldosterone
7.	Changing levels of vasopressin
8.	Changing levels of insulin
9.	Changing levels of sympathetic nervous system activation
10.	Changing levels of atrial natriuretic hormone

of the renin–angiotensin–aldosterone system, and the sympathetic nervous system are the three most likely factors responsible for the altered renal-function curves observed in obesity.

Insulin Resistance

For years it has been recognized that hypertension is common in both obese and diabetic individuals. Glucose intolerance, independent of obesity, is also associated with hypertension *(57)*. In children, several studies have demonstrated a positive association

between fasting insulin level and resting blood pressure *(58–62)*. Analysis of data from the San Antonio Heart Study has demonstrated an impressive pattern of overlap among hypertension, diabetes, and obesity. It has been estimated that by the fifth decade of life 85% of diabetic individuals are hypertensive and obese, 80% of obese subjects have abnormal glucose tolerance and are hypertensive, and 67% of hypertensive subjects are both diabetic and obese *(8,63)*. The relationship between insulin resistance and blood pressure has been observed in most populations *(64–67)*. Many investigators have suggested that insulin resistance may be the metabolic link that connects obesity to hypertension.

Factors known to improve insulin resistance are also associated with reductions in blood pressure. Weight loss has been documented to be associated with both a decrease in blood pressure and an improvement in insulin sensitivity *(68,69)*. The decline in blood pressure associated with exercise training programs seems to be limited to individuals who are initially hyperinsulinemic and have the greatest fall in plasma insulin level as a result of the training program *(69,70)*.

In addition to human data linking insulin and blood pressure, there are also animal data that suggest that insulin is an important regulator of blood pressure *(18,19,71–78)*.

Finally, there is evidence to suggest that in normal weight individuals, hyperinsulinemia and insulin resistance precede the development of hypertension. Young black males with borderline high blood pressure have higher insulin levels and more insulin resistance than normotensive black men *(64,65)*. In the Tecumseh Study *(79)*, individuals with borderline hypertension have higher plasma insulin levels and greater weight than normotensive individuals. Normotensive children with a family history of hypertension have higher insulin levels and more insulin resistance than children with no family history of hypertension *(80)*.

With respect to hypertension, one of the potentially important actions of insulin is the ability to induce renal sodium retention. Insulin resistance and/or hyperinsulinemia can result in chronic sodium retention. Insulin can enhance renal sodium retention both directly, through its effects on renal tubules *(81–83)*, and indirectly, through stimulation of the sympathetic nervous system and augmenting angiotensin II-mediated aldosterone secretion *(84,85)*. There are data to suggest that insulin resistance is directly related to sodium sensitivity in both obese and non-obese subjects. Rocchini et al. *(33)* demonstrated in obese adolescents that insulin resistance and sodium sensitivity of blood pressure are directly related. They demonstrated that the blood pressure of obese adolescents is more dependent on dietary sodium intake than the blood pressure of non-obese adolescents and that hyperinsulinemia and increased sympathetic nervous system activity appear to be responsible for the observed sodium sensitivity and hypertension. Finta et al. *(86)* showed that the endogenous hyperinsulinemia that occurs in obese subjects following a glucose meal can result in urinary sodium retention. In that study, the investigators also demonstrated that the obese adolescents who were the most sodium sensitive had significantly higher fasting insulin concentrations, higher glucose-stimulated insulin levels, and greater urine sodium retention in response to the oral glucose load. Finally in non-obese subjects with *(87)* or without *(83)* essential hypertension, there is a direct relationship between sodium sensitivity and insulin resistance.

There are also animal data that suggests that insulin resistance may be partly responsible for the sodium retention associated with obesity hypertension. In a dog model of obesity-induced hypertension, Rocchini et al. *(18,19)* demonstrated that during the first week of the high-fat diet, the increase in sodium retention appeared to best relate to an increase in plasma norepinephrine activity; whereas, during the latter weeks of the high-fat diet, an increase in plasma insulin appeared to be the best predictor of sodium retention.

In non-insulin-resistant subjects, both a concomitant decrease in proximal tubular sodium reabsorption and an increase in glomerular filtration oppose the direct effect of insulin to increase distal sodium retention. Hall and co-workers *(53)* demonstrated that obesity-induced hypertension in the dog is associated with increased renal tubular sodium reabsorption. Ter Maaten et al. *(88)* demonstrated that insulin-mediated glucose uptake was positively correlated with changes in glomerular filtration but not with changes in either proximal tubular sodium reabsorption or overall fractional sodium excretion. They speculated that insulin could only cause abnormal sodium retention if an additional antinatriuretic stimulus is present, such as through stimulation of the sympathetic activity, or augmenting angiotensin II-mediated aldosterone production.

In addition to sodium retention, selective insulin resistance may modulate the development of hypertension through changes in vascular structure and function, alterations in cation flux, activation of the renin–angiotensin–aldosterone system, and activation of the sympathetic nervous system.

However, in contrast to these and other reports *(8,64–69,89–92)* linking hyperinsulinemia to hypertension there have been other studies that have been unable to establish a relationship between hyperinsulinemia and high blood pressure. There is at least one study in obese hypertensive individuals *(93)*, which did not find a correlation between hyperinsulinemia and hypertension. In normal dogs, a chronic infusion of insulin, with or without an infusion of norepinephrine, failed to increase blood pressure *(25,94)*. In addition, even in those reports that have documented a relationship between insulin and blood pressure there is significant overlap in insulin resistance between those individuals who are hypertensive and those who are normotensive. No correlation has been found between blood pressure and plasma insulin or insulin sensitivity in Pima Indians *(95)*. Finally, we observed that when fat-fed dogs were treated with aspirin, an inhibitor of NF kappa B activation, insulin resistance did not develop as the dogs become obese, but the dogs still developed hypertension. Similarly, when fat-fed dogs were treated with alpha- and beta-blockade, using prazosin and atenolol, hypertension did not develop as the dogs become obese, but the dogs still developed insulin resistance *(96)*. Thus, from all of these studies it is clear that not all hypertensive subjects are insulin resistant and not all insulin-resistant subjects are hypertensive; therefore, hyperinsulinemia and/or insulin resistant is not either the major or sole mechanism responsible for the altered renal pressure–natriuresis relationship observed in obesity.

Renin–Angiotensin–Aldosterone System

The renin–angiotensin–aldosterone system is an important determinant of efferent glomerular arteriolar tone and tubular sodium reabsorption. Its activity is modulated by dietary salt ingestion, blood pressure, and the sympathetic nervous system. Therefore, alterations in the renin–angiotensin–aldosterone system could be expected to alter pressure–natriuresis. Enhanced activity of the renin–angiotensin–aldosterone system has been reported in obese humans and dogs *(32,85,97–102)*. Granger and co-workers *(102)* reported that plasma renin activity is 170% higher in obese dogs than in control dogs.

Aldosterone concentrations have been demonstrated to be abnormal in both human and animal obesity *(32,97–101)*. For example, Rocchini et al. *(97)* demonstrated that compared to non-obese adolescents, obese adolescents had significantly higher supine and 2-h upright aldosterone concentrations. Although plasma renin activity was not significantly different between the two groups of adolescents, they observed that a given increment in plasma

renin activity produced a greater increment in aldosterone in the obese adolescents. Compared with an obese control group, weight loss resulted in both a significant decrease in plasma aldosterone and a significant decrease in the slope of the posture-induced relation between plasma renin activity and aldosterone. Goodfriend and Calhoun *(103)* suggested that increased plasma free fatty acids produced in obese individuals may stimulate aldosterone production independent of renin.

Insulin also has been shown to influence the renin–angiotensin–aldosterone system in both normal subjects *(84,104)* and in patients with diabetes *(105)*. For example, Rocchini et al. *(85)* measured the increase in plasma aldosterone after graded increases in intravenous angiotensin II before and after euglycemic hyperinsulinemia in seven chronically instrumented dogs. Euglycemic hyperinsulinemia resulted in a significantly greater ($p<0.01$) change in the angiotensin II-stimulated increments of plasma aldosterone than was observed when angiotensin II was administered alone. However, there was no dose dependence of insulin's effect on angiotensin II-stimulated aldosterone. In addition, although weight gain significantly increased angiotensin II-stimulated aldosterone. These authors speculated that increased plasma aldosterone concentration in some obese subjects maybe caused by increased adrenal sensitivity to angiotensin II.

Despite these results suggesting that obesity is associated with significant alterations in the renin–angiotensin–aldosterone system, Hall et al. *(53)* demonstrated that weight-related changes in blood pressure can occur in dogs independent of changes in angiotensin II, and de Paula et al. *(106)* demonstrated that the aldosterone antagonist, eplerenone, attenuated but did not prevent the sodium retention and hypertension associated with feeding dogs a high-fat diet. Thus, although the renin–angiotensin–aldosterone system may play an important role in the pathogenesis of obesity hypertension, it is not either the major or sole mechanism responsible for the altered renal pressure–natriuresis relationship observed in obesity.

Sympathetic Nervous System

For over 20 years it has been recognized that diet affects the sympathetic nervous system. Fasting suppresses sympathetic nervous system activity; whereas, overfeeding with either a high carbohydrate or high-fat diet simulates the sympathetic nervous system *(107–110)*. Insulin is believed to possibly be the signal that networks dietary intake and nutritional status to sympathetic activity. Glucose and insulin sensitive neurons in the ventromedial portion of the hypothalamus have been demonstrated to alter the activity of inhibitory pathways between the hypothalamus and the brain stem *(111)*. It has also been hypothesized that the physiological consequence of the link between dietary intake and sympathetic nervous system activity is to regulate energy expenditure in a hope to maintain weight homeostasis. Euglycemic hyperinsulinemia in both normal and obese humans and animals causes activation of the sympathetic nervous system as documented by increases in heart rate, blood pressure, and plasma norepinephrine *(30,85,112–115)*. Hyperinsulinemia is associated not only with an increase in circulating catecholamines but also with an increase in sympathetic nerve activity *(116)*. Landsberg and Krieger *(112)* suggested that in obese individuals the sympathetic nervous system is chronically activated in an attempt to prevent further weight gain, and that hypertension and other adverse cardiovascular effects of obesity are byproducts of the overactive sympathetic nervous system.

The Bogalusa Heart Study reported in a biracial group of children that resting heart rate was positively correlated with blood pressure and subscapular skinfold thickness *(117)*.

These investigators also demonstrated that a hyperdynamic cardiovascular state was associated with obesity *(118)*. Obese children are also reported to have increased heart rate variability and blood pressure variability as compared to non-obese children *(119)*. Microneurography, which directly measures sympathetic traffic to skeletal muscle, has consistently shown to be increased in obesity *(120)*.

Although many studies in obese individuals have demonstrated increased sympathetic nervous system activity, this has not been a universal finding *(121)*. Part of the controversy regarding the role of the sympathetic nervous system in obesity relates to relying on plasma levels of catecholamines as the index of sympathetic activity. Plasma norepinephrine levels provide an indirect assessment of systemic sympathetic activity, since they reflect the net balance between norepinephrine appearance and removal mechanisms and provide no information concerning what happens to norepinephrine after it is release from presynaptic sympathetic nerve terminals. Data from the Normative Aging Study *(41)* strongly suggest that obesity is associated with increased sympathetic nervous system activity. This study demonstrated that sympathetic activity, assessed by measuring 24-h urinary norepinephrine excretion, is directly related to abdominal girth, waist-to-hip ratio, and body mass index.

Previous studies in obese subjects have reported a positive association between sympathetic activity and increased blood pressure. In the fat-fed dog, Kassab et al. *(122)* demonstrated that renal denervation prevents both the sodium retention and the hypertension associated with weight gain but does not prevent insulin resistance. In addition, Eikelis et al. *(123)* using regional analysis of NE kinetics demonstrated increased renal NE spillover in obese subjects. In both animal and human studies, pharmacologic blockade of the sympathetic nervous system prevents the increase in blood pressure and sodium retention associated with obesity *(124,125)*. Finally, Lohmeier et al. *(126)* demonstrated that fat feeding of dogs causes a marked increase in the activity of the protein product of the immediate early gene *c-foss* in the baroreceptor sympathoexcitatory cells in the rostral ventrolateral medulla, a site known to be affected by both angiotensin II and leptin. Lohmeier's observations in obese dogs support the observations that sympathetic activity to the kidney and other vascular beds is increased in obesity hypertension *(122,123)*. Thus, activation of the sympathetic nervous systems appears to be one of the major factors responsible for both the altered renal-function relationship and hypertension observed in obesity. However, what is still unknown is what is the factor or factors responsible for activation of the sympathetic nervous system in obesity.

POSSIBLE MECHANISMS RESPONSIBLE FOR ACTIVATION OF THE SYMPATHETIC NERVOUS SYSTEM IN OBESITY

Since increased VAT appears to be the best predictor of hypertension *(3)*, it is likely that increased sympathetic activation is related to the metabolically active adipose tissue found in the visceral region. Visceral adipose tissue is known to secrete free fatty acids (FFAs), adipocytokines, and inflammatory cytokines into the portal circulation. Three possible mechanisms that may be responsible for the increase in sympathetic nervous system activity associated with obesity are increased FFA levels in the portal circulation, increased adipocytokines and inflammatory cytokine levels in the portal circulation, and/or central activation of the hypothalamic–sympathetic axis.

Increased Portal FFA and Increased Sympathetic Activation

Increased portal FFA may increase sympathetic activity through the development of insulin resistance and hyperinsulinemia. Arner *(127)* first suggested that the release into the portal vein of FFAs originating from the visceral fat might be responsible for the development of insulin resistance. There are a number of reports demonstrating that increasing FFAs by the infusion of a lipid emulsion leads, within hours, to substantial insulin resistance. Griffin et al. *(128)* demonstrated that FFAs interfere with insulin signaling at the level of a serine kinase cascade involving protein kinase C-θ, leading to defects in insulin signaling and glucose transport. Kabir et al. *(129)* demonstrated, in dogs fed a moderate-fat diet for 12 weeks, increased gene expression promoting lipid accumulation and lipolysis in visceral fat, as well as elevated rate-limiting gluconeogenic enzyme expression in the liver as evidence in favor of the portal FFA hypothesis.

Many investigators have documented that euglycemic hyperinsulinemia in both normal and obese humans and animals causes activation of the sympathetic nervous system as documented by increases in heart rate, blood pressure, and plasma norepinephrine *(85,112,116)*. However, it is unlikely that in obesity either hyperinsulinemia or insulin resistance is responsible for activation of the sympathetic nervous system or the subsequent development of hypertension since in the obese dog, Rocchini and co-workers *(96)* have demonstrated that insulin resistance and hypertension are dissociated from each other. Finally, in humans, long-term weight loss induced by bariatric surgery corrects the insulin resistance and hyperinsulinemia but does not prevent the hypertension *(39)*.

A second explanation for how increased portal FFAs could lead to activation of the sympathetic nervous system is that there is a known feedback mechanism relating FFA production and the sympathetic nervous system, whereby delivery of FFAs into the circulation results in sympathetic activation and conversely, sympathetic activity stimulates lipolysis. Grekin et al. *(130)* demonstrated that chronic portal venous infusion of an oleate solution and other long-chain fatty acids have a pressor effect that is mediated by the α-adrenergic component of the sympathetic nervous system. Thus, increased portal FFAs could be responsible for the initiation of both the hypertension and the insulin resistance associated with obesity.

Increased Inflammatory Cytokine Levels in the Portal Circulation Leading to Increased Sympathetic Activation

Visceral fat secretes substances like [TNF-α, IL-6, or decreased adiponectin] that may induce both insulin resistance and activation of the sympathetic nervous system. TNF-α and other proinflammatory cytokines elicit a broad spectrum of biological responses via their peripheral and central nervous system effects (Fig. 4). Because blood-borne cytokines are too large to readily cross the blood–brain barrier one possible route by which circulating cytokines might stimulate sympathetic activation is through activation of visceral sensory afferent nerves, particularly the abdominal vagus *(131)*.

Adipocytokines secreted from visceral fat may also play a role in the sympathetic activation associated with obesity. Both low levels of ghrelin and adiponectin have been reported to be associated with hypertension. Lin et al. *(132)* showed that ghrelin acts in the nucleus of the solitary tract to suppress renal sympathetic activity and to decrease arterial pressure.

In summary, the potential role of abdominally derived inflammatory cytokines and adipocytokines in obesity hypertension and activation of the sympathetic nervous system

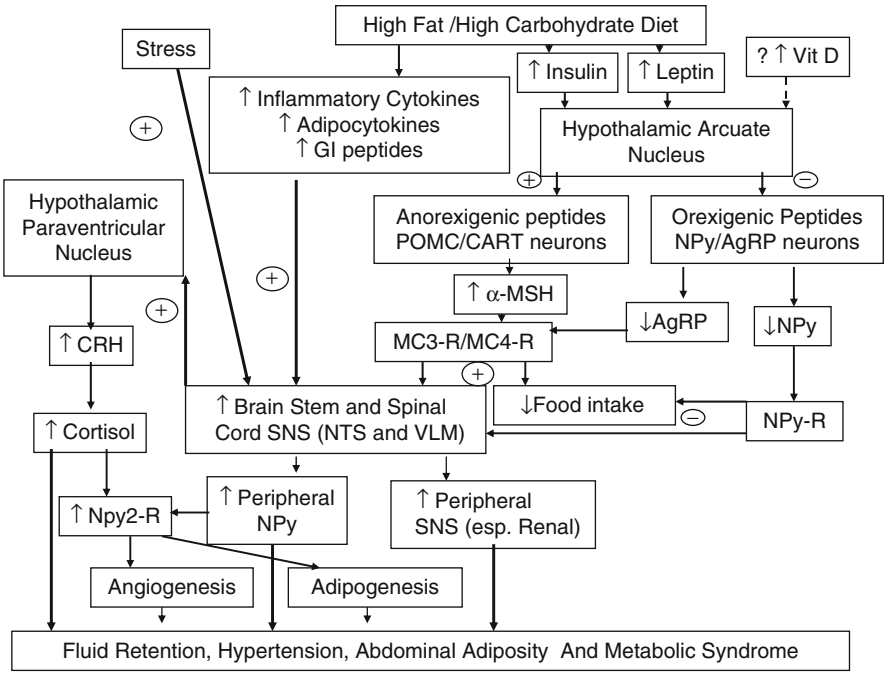

Fig. 4. A schematic representation of how ingestion of a diet high in fat and carbohydrates may be responsible for activation of the central and peripheral sympathetic nervous system (SNS) leading to the development of hypertension, abdominal adiposity, and the metabolic syndrome. The three locations in the central nervous system that are directly linking to central regulation of sympathetic activity are the hypothalamic arcuate nucleus, the hypothalamic paraventricular nucleus, and noradrenergic brain stem neurons in the nucleus tractus solitarii (NTS) and the ventrolateral medulla (VLM). A high-fat and carbohydrate diet through production of insulin and leptin can directly stimulate the arcuate nucleus to activate neurons expressing the anorexigenic peptides pro-opiomelanocortin (POMC) and cocaine-and amphetamine-regulated transcription (CART) and inhibition of neurons expressing the orexigenic peptides neuropeptide y (NPy) and agouti-related protein (AgRP). The resultant increase in production of alpha-melanocyte-stimulating hormone (α-MSH) and receptors (MC3-R/MC4-R) and the inhibition of production of AgRp and NYy and its receptors (NPy-R) results in both reduction in food intake and stimulation of the brain stem and spinal cord (SNS). Similarly, a diet high in fat and carbohydrates and /or stress can directly stimulate the NTS and VLM through production of inflammatory cytokines, adipocytokines, and gastrointestinal (GI) peptides. Once the NTS and VLM are activated, it can directly result in systemic activation of the SNS and the release of NPy leading to fluid retention and hypertension. The NTS and VLM through neural projections into the paraventricular nucleus of the hypothalamus result in release of corticotrophin-releasing hormone (CHR) and ultimately the production of cortisol from the adrenal gland that can both directly result in fluid retention, hypertension, and increased accumulation of abdominal fat or indirectly increasing the production NPy2-R that result in both increased angiogenesis and adipogenesis in abdominal fat.

remains controversial because of the limited amount of available data on the interaction between these substances and arterial pressure.

Activation of the Hypothalamic–Sympathetic Axis

The arcuate nucleus of the hypothalamus is a critical integrative center for the modulation of food intake and energy expenditure *(133)*. The arcuate nucleus contains at least two populations of neurons that have opposite influences on food intake and

energy expenditure. One population expresses the anorexigenic precursor peptides pro-opiomelanocortin (POMC) and the cocaine- and amphetamine-regulated transcript (CART) peptides, whereas the other expresses the orexigenic peptides neuropeptide Y (NYP) and agouti-related protein (AgRP) (Fig. 4).

Leptin, a 167-amino acid hormone that is secreted exclusively by adipocytes, activates POMC-containing neurons to produce the anorexigenic peptide alpha-melanocyte-stimulating hormone (a-MSH) and reduces the release of orexigenic peptides NPY and AgRP *(134,135)*. Therefore, in the setting of excess food, the elevated leptin levels activate the anorexigenic and inhibit the orexigenic pathway. In addition, NPY/AgRP and POMC-containing neurons in the arcuate nucleus have direct projections to the paraventricular nucleus and to the lateral hypothalamus, both of which are implicated in autonomic nervous system regulation *(136,137)*.

Recent evidence from Eikelis and Esler *(138)* suggests that leptin may be the link between excess adiposity and increased cardiovascular sympathetic activity. Plasma leptin concentrations are known to correlate with the level of obesity. Eikelis et al. *(123)* using simultaneous arteriovenous blood sampling demonstrated that the increase in plasma leptin concentration in obese individuals is not from either the heart or from the portal circulation, but rather it is from peripheral adipose tissue and from the leptin produced in the brain and secreted into the systemic circulation.

Leptin and the sympathetic nervous system are intimately linked. There is a direct interaction between leptin and the sympathetic nervous system, leptin acting within the hypothalamus to cause activation of the central sympathetic outflow and stimulation of the adrenal medulla to release epinephrine. While leptin has been shown in animals to be associated with an increased sympathetic outflow to the kidney, adipose tissue, and skeletal muscle, Eikelis et al. *(123)* demonstrated in humans that of the measures of sympathoadrenal function tested, only total and renal norepinephrine spillover rates correlated with leptin secretion rate. These data and the report of Kassab et al. *(122)* that renal sympathetic denervation prevents the fluid retention and hypertension in the fat-fed dog are consistent with but does not prove the hypothesis that leptin may be a major factor responsible for the increase sympathetic activation observed in obesity. However, since leptin has been shown to be equally if not more correlated to SAT compared to VAT, leptin does not completely fit the observation of Fox et al. *(48)* that hypertension is more associated with VAT than SAT in obese individuals.

In addition to leptin, other central neuropeptides have been implicated in the development of obesity and hypertension. NPy is a peptide that is expressed in various regions of the nervous system including the hypothalamus, the amygdale, the hippocampus, the nucleus of the solitary tract, and peripheral sympathetic nerves. Npy plays an important role in several physiological functions including the regulation of feeding behavior through mediation of the actions of leptin and insulin, cardiovascular homoeostasis, regulation of the sympathetic nervous system, regulation of blood pressure, and control of the circadian rhythms. In addition to NPy being produced and released into the brain it is also produced and released into the systemic circulation from sympathetic nerves (Fig. 4). Systemically released NPy causes vasoconstriction, angiogenesis, and proliferation and differentiation of adipocyctes and endothelial cells. Kuo et al. *(139)* demonstrated that stress, such as exposure to cold or aggression, causes the systemic release of NPy from sympathetic nerves, which in turn upregulates NPy and its receptors in a glucocorticoid-dependent manner in abdominal adipose tissue leading to diet-induced obesity and the development of hypertension and the metabolic syndrome. In addition, these investigators demonstrated

that in stressed mice, fed a diet high in fat and sugar, blockade of NPy receptors with either using NPy receptor antagonists or using NPy fat-targeted knockout mice results in reduced abdominal fat and metabolic abnormalities. Thus, although centrally released NPy causes reduced central sympathetic activity and reduced blood pressure, when it is released peripherally through increased sympathetic nerve activity, NPy can cause vasoconstriction and hypertension. In addition, recent genetic association studies have demonstrated that the carriers of the T1128C polymorphism of the NPy gene have an increased prevalence of hypertension and cardiovascular disease *(140,141)*.

The precursor molecule POMC undergoes post-translational processing by prohormone convertases and generates the alpha-, beta-, and gamma-melanocyte-stimulating hormone (MSH) and adrenocorticotropin (ACTH). The importance of the melanocortin pathway in the regulation of food intake became evident after the characterization of the agouti obesity syndrome *(142)*. Alpha-MSH is the primary endogenous agonist for melanocortin receptors and plays an important role in the inhibition of food intake. Alpha-MSH has recently been shown to play a role in the regulation of blood pressure *(143,144)*.

Recently, vitamin D deficiency has been hypothesized as a cause of obesity and the metabolic syndrome *(145)*. Foss speculates that the metabolic and physiological changes observed as the metabolic syndrome, including hypertension and insulin resistance, could result from a "winter metabolism" which increases themogenic capacity. Foss speculates that the stimulus for the winter response is a fall in vitamin D due to reduced ultraviolet-B range sunlight exposure that occurs in mid-latitudes in autumn and winter. He proposes that a fall in circulating calcidiol is sensed in the hypothalamus and induces an increase in the body weight set point. A state of energy accrual ensues in which appetite is increased and energy expenditure reduced by activation of the AgRP/NPy neurons and inhibition of the POMC/CART neurons. The basis of this hypothesis is a body of evidence that demonstrates an inverse relationship between vitamin D status and both obesity and the metabolic syndrome *(146–149)*.

Finally, the similarities between Cushing's syndrome and the metabolic abnormalities associated with obesity hypertension have lead Bjorntrop and others to speculate that hypercortisolemia is involved in the pathogenesis of obesity hypertension *(150)*. There is evidence of increased secretion and turnover, resulting in normal or even lower than normal circulating concentration *(151)*. Measuring salivary cortisol, investigators have been able to demonstrate that normally regulated cortisol secretion is associated with "healthy" anthropometric, metabolic, and hemodynamic variables. However, upon perceived stress, cortisol secretion is increased and followed by insulin resistance, abdominal obesity, elevated blood pressure, and hyperlipidemia *(152,153)*. Rosmond and Bjorntrop *(154)* have demonstrated that diminished dexamethasone suppression is directly associated with obesity and elevation of leptin levels. Zahrezewska et al. *(155)* demonstrated in rats that glucocorticoids diminish leptin signals.

Bjorntorp and Rosmond *(150)* speculate that the two ways that elevated activity of the hypothalamic–pituitary adrenal axis could occur are either an elevated stimulation and/or a diminished feedback control. Elevated stimulation of the HPA axis can occur due to psychosocial and socioeconomic handicaps such as living alone, divorce, poor education, low social class, family member on unemployment, and problems at school, or even due to excess food intake *(156)*. With respect to causes of diminished feedback control of the HPA axis, Bjorntorp and others *(157–159)* demonstrated that a restriction fragment length polymorphism of the glucocorticoid receptor gene is associated with poorly controlled HPA axis function, as well as abdominal obesity, insulin resistance, and hypertension. Finally Kabir

et al. *(129)* has demonstrated in mice that the combination of stress and a diet high in fat and sugar results in increased secretion of glucocorticoids which act as an upstream modulator of NPy activity. The increased activity of NPy and the NPy2 receptor is ultimately responsible for the development of obesity, hypertension, and the metabolic syndrome.

Therefore, Bjorntorp has suggested that many of the cardiovascular and physiologic consequences found in obese individuals could be due to "a discretely elevated cortisol secretion, discoverable during reactions to perceived stress in everyday life" *(160)*.

Summary

In summary, based on animal and human data, the best hypothesis for the mechanism of obesity hypertension is that ingestion of diet high in fat and sugar results in both increasing abdominal adiposity and activation of the hypothalamic–sympathetic axis. The combination of an increase in portal levels of FFA, increased secretion from visceral adipocytes of both adipocytokines (such as leptin) and inflammatory cytokines, stress and/or potentially even vitamin D deficiency is most likely responsible for the central activation of the hypothalamic–sympathetic axis. Activation of the hypothalamic–sympathetic axis produces increased renal sympathetic, activation of the renin–angiotensin–aldosterone system, fluid retention and ultimately in the development of systemic hypertension (Fig. 4).

OBESITY AS A CARDIOVASCULAR RISK FACTOR

The Framingham Heart Study *(5)* identified obesity and hypertension as independent risk factors for the development of cardiovascular disease. Obese normotensive and hypertensive men have a higher rate of coronary heart disease *(47)*. Manson et al. *(161)* has also reported that in women, the relative risk of fatal and nonfatal coronary heart disease increased from the lowest to the highest quartiles of obesity. Childhood obesity is associated with the development of early coronary artery pathology. The autopsies of 210 children aged 5–15 years who had suffered violent death were evaluated by Kotelainen *(162)*. Ponderal index was a significant predictor of heart weight and the presence of coronary artery intimal fatty streaks. In the Bogalusa Heart Study, Berenson et al. demonstrated that children and young adults who died of trauma showed an association between body mass index, systolic and diastolic blood pressure, and the presence of fatty streaks and fibrous plaques in the aorta and coronary arteries *(15,61)*. Recently Inge et al. *(163)* reported that following surgically induced weight loss adolescents experienced remission of type 2 diabetes and improved serum lipids and blood pressure.

Long-standing obesity is associated with preclinical and clinical left ventricular dilation *(164)* and impaired systolic function *(165,166)* with heart failure, frequently being the ultimate cause of death in markedly overweight individuals *(167)*.

A physiological change that may contribute to the association of obesity with left ventricular dilatation is sodium retention and a concomitant increase in blood volume and cardiac output. Many investigators *(168)* have reported that obesity is associated with an increased blood volume and cardiac output. However, the increment in cardiac output associated with obesity cannot be explained by an increase in adipose tissue perfusion alone; some have suggested that blood flow to the non-adipose mass must also be increased in obese subjects *(169,170)*. Thus, obesity is characterized by a relative volume expansion in the presence of restricted vascular capacity. The increase in volume in the presence of restricted vascular capacity may lead to left ventricular dilatation, increased left ventricular wall stress, and

compensatory left ventricular hypertrophy *(165,169,170)*. Hypertension increases afterload and as a consequence the left ventricle adapts with an increase in wall thickness. The combination of obesity and hypertension therefore creates a double burden on the heart, ultimately leading to the development of impaired ventricular function *(165–167,171,172)*.

MacMahon et al. *(164)* reported that 50% of individuals who are more than 50% overweight have left ventricular hypertrophy. In children, adiposity is also one of the determinants of left ventricular mass. Urbina et al. reported that the major factors influencing left ventricular mass in childhood were linear growth, defined by height and measures of ponderosity *(173)*. Daniels et al. reported that in children, lean body mass was the strongest determinant of left ventricular mass, but that fat mass and systolic blood pressure were also important predictors of left ventricular mass *(174,175)*. As with blood pressure, weight loss can result in regression in the left ventricular hypertrophy *(164,176,177)*. More recently, Ippisch et al. *(178)* demonstrated that surgically induced weight loss in morbidly obese adolescents resulted in a significant improvement in left ventricular mass and geometry, diastolic function, and cardiac workload.

Unlike the universal finding of left ventricular hypertrophy in obese individuals, not all studies have demonstrated impairment in left ventricular function. Schmeider and Messerli *(179)* reported that obese hypertensive individuals have normal global left ventricular systolic function as measured by left ventricular fractional shortening and velocity of circumferential fiber shorting. However, since both of these indices of left ventricular systolic function are dependent on ventricular preload and afterload, the results of Schmeider's study do not document that left ventricular contractility is normal. In fact, Blake and co-workers *(176)* demonstrated that despite a normal left ventricular ejection fraction at rest, obese individuals have an impaired left ventricular ejection fraction in response to dynamic exercise. Guillerno et al. *(171)* reported that the end-systolic wall stress to end-systolic volume index, a load-independent index of left ventricular function, is also abnormal in even mild or moderately obese individuals. These investigators also documented a significant inverse relationship between the index of end-systolic wall stress to end-systolic volume index and body mass index, diastolic diameter, and left ventricular mass index.

Abnormalities in left ventricular filling have also been reported to occur in obese individuals, i.e., decreased peak filling rate, duration of peak filling and left atrial emptying index *(176)*, an increased isovolumic relaxation time, and an abnormal mitral valve Doppler filling pattern *(172)*. Harada et al. *(180)* demonstrated that body mass index predicts left ventricular diastolic filling rate in asymptomatic obese children. Kanoupalis et al. *(181)* and Ippisch et al. *(178)* demonstrated that weight loss improves diastolic function.

The left ventricular hypertrophy, depressed myocardial contractility, and diastolic dysfunction can predispose individuals to excessive ventricular ectopy. Messerli et al. *(182)* reported that the prevalence of premature ventricular contractions was 30 times higher in obese individuals with eccentric left ventricular hypertrophy than in lean individuals.

Finally, as with hypertension, insulin resistance may be related to both the cardiac hypertrophy and abnormal cardiac function that is observed in many obese individuals. Nakajima et al. *(183)* reported that there is a direct relationship between intraabdominal fat accumulation and the cardiac abnormalities associated with obesity. Since increased upper body and intraabdominal fat accumulation relates to the presence of insulin resistance even without significant overall obesity, these investigators speculated that the cardiac dysfunction observed in obese individuals may be related to insulin resistance.

SUMMARY

Obesity is recognized as an independent risk factor for the development of cardiovascular disease. Obesity in both children and adults is associated with the development of cardiac dysfunction. Obese individuals have an increased risk for developing left ventricular dilatation, impaired systolic and diastolic dysfunction, and the development of left ventricular hypertrophy (Table 2).

Table 2
Cardiovascular Consequences of Obesity

1. Premature development of coronary atherosclerosis
2. Left ventricular hypertrophy
3. Left ventricular dilation
4. Left ventricular diastolic dysfunction
5. Left ventricular systolic dysfunction
6. Congestive heart failure

MANAGEMENT OF THE OBESE CHILD WITH HYPERTENSION

Weight loss is the cornerstone of hypertensive management in the obese individual. Weight loss in both adolescents and adults improves all of the cardiovascular abnormalities associated with obesity, including hypertension, dyslipemia, and sodium retention, structural abnormalities in resistant vessels, and left ventricular hypertrophy and dysfunction. It is also important to realize that the method by which weight loss is accomplished is important. Although weight loss in general results in a drop in resting systolic/diastolic blood pressure and heart rate, the greatest decrease in resting systolic blood pressure, peak exercise diastolic pressure, and heart rate can be achieved when the weight loss is incorporated with physical conditioning *(30)*. Similarly, a weight loss program that incorporates exercise along with caloric restriction produces the most favorable effects on insulin resistance *(30,70)*, dyslipidemia *(70,184)*, and vascular reactivity *(30,185)*. Endurance training in obese and non-obese individuals improves insulin resistance, in part, by increasing muscle oxidative capacity and increasing capillary density *(186,187)*. Most investigators believe that the additive effect of exercise to weight loss is related to the fact that exercise improves insulin resistance independent of weight loss.

In the morbidly obese adolescent, surgically induced weight loss also is accompanied by both an improvement in type 2 diabetes and a marked reduction of both blood pressure and other cardiovascular risk factors *(163,178)*.

Although weight loss and exercise are the cornerstones of blood pressure management in obese hypertensive individuals, most obese individuals are either unable or unwilling to lose weight or are unable to keep from regaining lost weight. Therefore, pharmacological therapy is frequently required in the hypertensive obese individual. The pharmacologic therapy of the obese hypertensive is divided into treatment of obesity and/or treatment of hypertension. The role of drug therapy in the treatment of childhood obesity is controversial. Many of the obesity drugs that have been tried in adults have resulted in complications, such as pulmonary hypertension and tricuspid regurgitation with fenfluramine/dexfenfluramine *(188)*. There have been few well-controlled studies to show that the available obesity drugs

are well tolerated and effective for use in obese children. One medication that is currently approved for the treatment of obesity in adolescents is sibutramine, an inhibitor of reuptake of serotonin and norepinephrine. Although sibutramine is also associated with an increase in blood pressure in some patients, Daniels et al. *(189)* demonstrated that blood pressure decreased with sibutramine-induced weight loss in obese adolescents *(189)*. Orlistat is a gastrointestinal lipase inhibitor that is a safe and effective pharmacological treatment for childhood obesity *(190)*. Weight loss associated with Orlistat is associated with a decrease in blood pressure and other cardiovascular risk factors *(191)*.

In addition to the use of comprehensive, multidisciplinary weight loss programs and drugs, there also are new investigational strategies that can be used to treat obesity and it metabolic consequences. Wang et al. *(192)* recently reviewed the results of acupuncture in the treatment of obesity. These investigators demonstrated in a rat experimental model of obesity that electroacupuncture produced a significant reduction of both food intake and body weight as well as a reduction in lipids and other cardiovascular risk factors. They demonstrated that electroacupuncture stimulation produced an increased expression of the anorexigenic peptides α-MSH and CARR and a decreased expression of the orexigenic peptide NPy in the arcuate nucleus of the rat hypothalamus (Fig. 4). They also reported an open trial in 16 overweight humans which demonstrated that electrical acupoint stimulation produces a steady and significant decrease of body weight.

Experimental studies have shown that overactivation of the endocannabinoid (CB) system, a physiologic signaling system involved in regulating energy intake, fatty acid synthesis and storage, and glucose and lipid metabolism is associated with obesity, dyslipidemia, hypertension, and insulin resistance *(193)*. In clinical trials, rimonabant, the first selective CB1 receptor blocker, has resulted in substantial weight loss and significant improvement in lipid profiles and blood pressure *(194–196)*. The most commonly reported adverse events associated with rimonabant were nasopharyngitis, headache, back pain, nausea, influenza, and arthralgia. However, the most commonly associated reason for discontinuation of therapy was depressed mood disorders observed in 2.3–3.7% of patients. No trial of rimonabant has been reported in children and adolescents.

Finally, metformin is an older drug that has found new life in the treatment of obesity. For adolescents with morbid obesity and insulin resistance, including women with polycystic ovarian syndrome, the addition of metformin to a multidisciplinary weight loss program not only improved insulin resistance and lipid levels but also significantly reduced weight and body mass index *(197)*. Helvaci et al. *(198)* reported that the administration of metformin in 324 individuals with white-coat hypertension, only 279 who were overweight or obese, resulted in significant weight loss, improvement in there lipid profiles, and resolution of their white-coat hypertension. Thus, metformin appears to be an effective treatment not only of insulin resistance but also of white coat hypertension.

When choosing an antihypertensive agent for the obese child, it is important to remember that depending on the antihypertensive agents used, insulin resistance has been reported to improve, worsen, or remain unchanged. In general, thiazide diuretics *(92,199,200)* and β-blockers *(192,199)* are known to impair insulin sensitivity and glucose tolerance; calcium blockers do not seem to adversely affect carbohydrate metabolism *(201–203)*; indapamide and potassium-sparing diuretics do not influence glucose homeostasis *(204)*; and finally, angiotensin-converting enzyme inhibitors *(199)*, angiotensin II receptor blockers *(205)*, and α_1-blockers *(206,207)* may even improve glucose metabolism and insulin resistance. Recently, Rocchini et al. *(124)* demonstrated that clonidine, a centrally acting sympathetic agent, not only improved the hypertension associated with obesity but also improved the

insulin resistance. Giugliano et al. *(208)* demonstrated that transdermal clonidine was effective in reducing blood pressure and improving insulin resistance in hypertensive individuals with non-insulin-dependent diabetes mellitus. Based on these two preliminary studies, it would appear that clonidine or other like drugs have a favorable profile for obese individuals with hypertension.

In addition to their unfavorable effect on insulin resistance, thiazide diuretics impair pancreatic insulin secretion *(209,210)* and increase LDL cholesterol and total cholesterol *(111,211)*. β-blockers are associated with a two- to threefold incidence of inducing diabetes mellitus *(212)* and are associated with a significant lowering of HDL cholesterol *(213,214)*. However, despite the different pharmacologic profiles of the antihypertensive drugs, there exists no clear recommendation for obese hypertensive individuals.

There is increasing data that confirm that angiotensin-converting enzyme inhibitors have specific benefit in individuals with diabetes, atherosclerosis, left ventricular dysfunction, and renal insufficiency *(215)*. In addition, one of the angiotensin receptor blockers, telmisartan has peroxisome proliferator-activated receptor-γ (PPAR-γ) activity. When compared to candesartan, telmisartan resulted in greater weight loss and more improvement in glucose tolerance in hypertensive patients with glucose intolerance. Telmisartan appears to have uniquely beneficial properties in individuals with obesity hypertension and the metabolic syndrome *(216)*.

Finally, there is one other class of agents, thiazolidinediones (pioglitazone, rosiglitazone, and troglitazone) that also appear to reverse insulin resistance, hypertension, and dyslipemia *(217,218)*. However, troglitazone recently has been associated with significant liver toxicity and fluid retention *(219)*. It is too early to know the role that these or similar agents will have in the treatment of childhood obesity hypertension.

SUMMARY

Although weight loss is the cornerstone of hypertensive management in the obese individual, many individuals will also require pharmacologic therapy. When choosing an antihypertensive medication, it is important to individualize the agent to the patient. Some agents such as thiazide diuretics and β-blockers can impair glucose tolerance and adversely alter plasma lipid levels. Whereas, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and centrally acting sympathetic agents improve both the hypertension and the insulin resistance associated with obesity. Finally, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are also effective in reducing the development of congestive heart failure and reducing cardiovascular mortality.

FUTURE PERSPECTIVES

The prevalence and severity of obesity is increasing in children and adolescents. Based on this increased incidence of childhood obesity, we are currently facing an epidemic of childhood type II diabetes and hypertension *(220)*. In the past, most pediatricians have been taught that hypertension in children is a rare condition associates with renal disease. In reality, secondary hypertension in children has become far less common relative to primary (essential) hypertension. In a large pediatric hypertension practice, the typical hypertensive child is an otherwise healthy adolescent with obesity and some combination of cardiovascular risk factors associated with obesity. Obesity in childhood is a chronic medical condition

and requires long-term treatment. It is hoped that with new discoveries more effective forms of treatment of childhood obesity will be developed.

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18 Hypertension in Children with the Metabolic Syndrome or Type 2 Diabetes

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Contents

INTRODUCTION

Of the many consequences of childhood obesity, the early development of type 2 diabetes (T2DM) is perhaps the most worrisome due to the long-term cardiovascular and renal sequelae of this condition. The metabolic syndrome (MS), a manifestation of insulin resistance that most commonly occurs in obese individuals, also has significant cardiovascular manifestations and commonly occurs in obese children and adolescents. This chapter reviews manifestations of hypertension in children with T2DM or the MS, with a significant focus on treatment considerations.

CLASSIFICATION OF BLOOD PRESSURE IN THE YOUNG

Traditional (hard) cardiovascular end points used to define levels of HTN in adults (myocardial infarction, stroke, etc.) do not occur in children and adolescents. Therefore, the definition of HTN in the young is a statistical one derived from analysis of a large database of BP obtained in healthy children and adolescents by screening projects such as

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_18
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Table 1
Classification of Hypertension in Children, Adolescents, and Adults

Blood pressure classification	*Children and adolescents (≤ 17years 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 90th–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 ≥95th–99th percentile plus 5 mmHg	SBP 140–159 mmHg or DBP 90–99 mmHg
Stage 2 hypertension	SBP or DBP >99th percentile plus 5 mmHg	SBP ≥160 mmHg or DBP ≥100 mmHg

DBP, diastolic blood pressure; SBP, systolic blood pressure
Adapted from *(1,2)*.

the NHANES. According to this approach, normal BP in children and adolescents is systolic and diastolic BP below the 90th percentile for age, gender, and height, while HTN is defined as systolic or diastolic BP persistently greater than the 95th percentile *(1)*. Tables that list normative BP values for adolescents ≤17 years of age have been published; these are available elsewhere in this text. For older adolescents ≥18 years of age, the adult BP classification scheme issued by the Joint National Commission *(2)* should be followed. A comparison of the pediatric and adult BP classification schemes is presented in Table 1.

Common to both the pediatric and adult BP classification schemes is the concept of "prehypertension." This refers to BPs that would have been classified as "high-normal" in prior consensus recommendations. While the term prehypertension has proven to be controversial, it is meant to serve as a means of alerting patients and physicians alike of the potential for later development of HTN, and of the need to make lifestyle changes that might prevent this from occurring. This is particularly important for obese individuals. The same BP value of >120/80 is used in both adolescents and adults to designate prehypertension.

HYPERTENSION IN THE METABOLIC SYNDROME

The MS is a constellation of metabolic risk factors for developing atherosclerotic cardiovascular disease and diabetes mellitus, including dyslipidemia, insulin resistance, central obesity, and HTN. The prevalence of the metabolic syndrome in adults has been found to be 21.8% and it 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)*. With 34% of the American adult population being overweight (body mass index [BMI] 25–29.9 kg/m^2), and 27% being obese (BMI ≥30 kg/m^2) *(4)*, the MS is becoming increasingly prevalent.

While it is clear that components of the MS can also be identified in children and adolescents, a consensus definition for the MS has been difficult to reach for the pediatric population. A common approach has been to apply modified ATP III criteria, requiring three or more of the following: serum triglycerides (TGs) >95th percentile, HDL cholesterol <5th

percentile, systolic or diastolic blood pressure (BP) >95th percentile, and impaired glucose tolerance *(5)*. Using these modified criteria, 39% of those who were moderately obese and 50% of those who were severely obese had the MS. The prevalence increased with increasing degrees of insulin resistance when adjusting for race and degree of obesity. Using more stringent criteria, the prevalence of MS in the NHANES III 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) *(6)*.

Recently, the International Diabetes Federation (IDF) Task Force on Epidemiology and Prevention of Diabetes has proposed a new consensus definition for the MS in childhood that utilizes different criteria for different age groups (Table 2) *(7)*. Central to this definition is the use of waist circumference to define risk. Waist circumference has recently been shown to be an independent predictor of insulin resistance, lipid levels, and blood pressure *(8)*; use of waist circumference percentiles in the proposed IDF definition is felt to account for changes associated with growth. It is unclear, however, why the IDF chose an absolute BP level instead of a BP percentile to denote elevated BP in the 6–16-year-old group. As has been pointed out in a recent review, this definition of the pediatric MS will require validation in large-scale studies before it can be widely adopted *(9)*.

Given that elevated BP is one of the criteria for diagnosis of the MS, it follows that the majority of individuals with the MS will exhibit some degree of BP elevation. The MS has been identified as a strong independent predictor of cardiovascular events in hypertensive individuals, amplifying the cardiovascular risk associated with HTN *(10)*. Recent studies indicate that the process of atherosclerosis starts at an early age and is already linked to obesity and other components of the MS in childhood *(11)*. This makes accurate identification and appropriate treatment of children and adolescents with the MS an important priority for our healthcare system.

Table 2
Proposed IDF Definition of MS in Children and Adolescents

Age 6 to <10 years
- Obesity ≥90th percentile as assessed by waist circumference
- Metabolic syndrome cannot be diagnosed, but further measurements should be made if family history of metabolic syndrome, type 2 diabetes mellitus, dyslipidemia, cardiovascular disease, hypertension, or obesity

Age 10 to <16 years
- Obesity ≥90th percentile (or adult cutoff if lower) as assessed by waist circumference
- Triglycerides ≥1.7 mmol/l
- HDL cholesterol <1.03 mmol/l
- Blood pressure ≥130 mmHg systolic or ≥85 mmHg diastolic
- Glucose ≥5.6 mmol/l (oral glucose tolerance test recommended) or known type 2 diabetes mellitus

Age >16 years
- Use existing IDF criteria for adults

HDL, High-density lipoprotein; IDF, International Diabetes Federation

HYPERTENSION IN TYPE 2 DIABETES

In adults with type 2 diabetes (T2DM), hypertension is common. Recent data from the NHANES 1999–2004 survey indicate that overall over 70% of prevalent adults with T2DM have coexisting hypertension, and that the prevalence has been increasing over the past decade *(12)*. Indeed, a significant proportion of adults with newly diagnosed T2DM are already hypertensive at the time of diagnosis *(13)*. Hypertension in adults with T2DM is often poorly controlled, with only about 30% of patients achieving the recommended target BP of <130/80 *(12)*. Consequently, there is a high rate of stroke and other severe cardiovascular disease in adults with T2DM, and premature death from cardiovascular causes is common *(14)*.

Not surprisingly, fewer data are available on the prevalence of hypertension in children and adolescents with T2DM. In a recent analysis of data from the SEARCH for diabetes in youth study, 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 vs. 73% among those with T2DM—however, there were fewer than 100 subjects with T2DM in the study sample *(15)*. Other reported prevalences of hypertension in youth with T2DM range from 8 to 36% *(16)*, which is certainly lower than in adults, but still greater than in unselected pediatric populations, even given the effects of the childhood obesity epidemic *(17)*. Some of these studies are characterized by use of nonstandard definitions of hypertension, or reliance on single measurements of BP, which limits the conclusions that can be made regarding prevalence.

In a study of obese minority adolescents with and without T2DM that incorporated ambulatory blood pressure monitoring (ABPM) *(18)*, we found ambulatory hypertension in 39% of those with T2DM, compared to only 8% of those without T2DM. Nearly all ABPM variables, including mean awake and sleep BP and awake and sleep BP loads *(19)*, were significantly higher in the T2DM subjects. 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. Of note, abnormal ambulatory BP profiles in youth with T2DM were accompanied by a high incidence of microalbuminuria *(18)*, suggesting that as in adults, there is early development of renal damage in pediatric patients with T2DM.

Clearly, better data are needed regarding the prevalence of hypertension and other cardiovascular risk factors in youth with T2DM. It is likely that given the increasing prevalence of T2DM in children and adolescents, particularly among specific minority groups *(20,21)*, large-scale studies can be conducted to prospectively study this important risk factor. 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.

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 Chapter 17. Additionally, discussions of this form of hypertension in adults *(14,22)* would also be pertinent to adolescents with either the MS or T2DM.

Insulin resistance is clearly the major pathophysiologic mechanism involved in the development of hypertension in both the MS and T2DM. Landsberg has noted that "...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 prohypertensive effect that, in susceptible individuals, causes hypertension" *(23)*. 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 abrogration of hypertension after adrenergic blockade *(24,25)*. While there are likely multiple mechanisms involved in activation of the SNS in the MS and T2DM *(26)*, 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, leading to hypertension through an expansion of plasma volume. Insulin increases renal sodium reabsorption, possibly in the distal nephron, although this is not completely certain *(27)*. It is likely that increased activity of renal sympathetic nerves is responsible at least in part for this effect *(28)*. Elevated circulating levels of aldosterone, which have been demonstrated in salt-sensitive obese adolescents, may also be involved *(29)*. Importantly, these effects of hyperinsulinemia on renal sodium handling can be reversed with weight loss *(29)*.

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 *(30)*, in hypertensive subjects this effect is probably offset by vasoconstriction mediated by increased sympathetic nervous activity *(30,31)*. In addition, impaired vasodilatation in response to insulin infusion has been demonstrated in obese individuals *(32)*. Alternatively, insulin may act to stimulate vascular smooth muscle proliferation in resistance vessels via activation of the local renin–angiotensin system *(33)*, 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 *(34)*.

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 Nonpharmacologic Therapy

(Also see Chapter 30.)

While the effects on BP may be modest in magnitude, weight loss, aerobic exercise, and dietary modifications have all been shown to successfully reduce BP in children and adolescents, and are therefore considered primary treatment in children with obesity-related

HTN *(1)*. Studies in obese adolescents have demonstrated that modest 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 *(35–37)*. In studies where a reduction in body mass index of about 10% 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 *(38)*. However, identifying a medical complication of obesity such as the MS or T2DM can perhaps 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 *(39)*. However, cessation of regular exercise is generally promptly followed by a rise in BP to preexercise levels. Aerobic exercise activities such as running, walking, or cycling are usually preferred to static forms of exercise in the management of HTN. Many children may already be participating in one or more appropriate activities and may only need to increase the frequency and/or intensity of these activities to produce a reduction in their BP. At the very least, the amount of time spent in sedentary activities such as television viewing should be restricted to <2 h/day *(40)*. Increasing physical activity may not only reduce BP, but can help with weight loss and/or maintenance, and has been proven to be effective in preventing the development of T2DM *(41)*.

For best results in terms of BP reduction and weight control, exercise should probably be combined with dietary changes such as those discussed below. Such an approach has been shown to improve markers of insulin resistance in obese adolescents *(41,42)*. The combination of dietary changes and exercise training may also improve vascular function in addition to reducing BP *(43)*.

Dietary modification in the management of HTN in children and adolescents has received a great deal of attention. Nutrients that have been examined include the obvious, such as sodium, potassium, and calcium, as well as folate, caffeine, and other substances. Manipulation of sodium intake has received extensive study *(44)*. Many authors have noted that the typical dietary sodium intakes of children and adolescents, at least in the United States, far exceed any nutritional requirements for sodium. Trials of dietary sodium restriction in hypertensive children and adolescents have had mixed results, with some studies showing no benefit, and others showing a modest reduction in BP in obese adolescents but not in lean adolescents *(29)*. This suggests that 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.

Other nutrients that have been examined in hypertensive children and adolescents include potassium and calcium, both of which have been shown to have antihypertensive effects. A recent 2-year trial of potassium and calcium supplementation in hypertensive, salt-sensitive Chinese children demonstrated that this combination significantly reduced systolic BP *(45)*. Therefore, a diet that is low in sodium and enriched with potassium and calcium may be more effective in reducing BP than a diet that restricts sodium only.

An example of such a diet is the so-called “DASH” diet, which has been shown to have an antihypertensive effect in adults with HTN, even in those receiving antihypertensive medication *(46,47)*. The basic elements of the DASH eating plan are logical to apply the treatment of hypertensive children, especially if accompanied by counseling from a

pediatric dietitian. A recent study in a population of mostly obese adolescents with either prehypertension or Stage 1 HTN confirmed that a DASH-type eating plan is effective in reducing BP in the young *(48)*. The DASH diet also incorporates higher intake of such micronutrients 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 Hypoglycemic Agents

It has become apparent over recent years that many of the agents used to improve insulin sensitivity in individuals with the MS or T2DM have important cardiovascular effects as well. Although treatment with these agents will not obviate the need for antihypertensive medications in most affected individuals, their potential impact on BP deserves 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 *(48–50)*. Studies in rats with streptozotocin-induced diabetes have demonstrated that metformin reduces BP and restores aortic endothelial function *(51)*. Human studies, however, have not uniformly demonstrated a significant effect of metformin on BP.

Manzella et al. randomized 128 subjects with T2DM to either metformin or placebo in order to examine 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 *(52)*. In another study, metformin was given for 12 weeks to obese subjects with T2DM managed with either 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 *(53)*. Finally, Stakos et al. randomized subjects 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 *(54)*. Clearly, metformin alone will be insufficient treatment for hypertension in the MS or T2DM, but it may have some beneficial cardiovascular effects.

Rosiglitazone, a thiazolidinedione, binds to the peroxisome proliferator-activated receptor-gamma (PPAR-γ), a transcription factor that regulates the expression of genes that involved in glucose production, transport, and utilization in the liver, adipose tissue, and muscle *(50)*. Rosiglitazone has been shown to improve vascular function and ameliorate BP in hypertensive transgenic mice *(55)*. Negro et al. compared the effects of rosiglitazone and metformin vs. metformin alone on BP and metabolic parameters of diabetic patients *(56)*. 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 *(57)*. Rosiglitazone has also been studied in combination with metformin with or without the addition of glimepiride, a second-generation sulfonylurea, in hypertensive type 2 diabetic patients *(58)*. Subjects were randomized to treatment with either metformin + glimepiride or

metformin + rosiglitazone. Mean BP was not significantly improved at any time in the group that received glimepiride + 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 *(58)*.

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 metformin + pioglitazone. After 8 weeks of treatment, the metformin + pioglitazone group had reduced nocturnal BP values which were independent of changes in metabolic parameters *(59)*.

Acarbose is a glucose oxidase inhibitor which 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 *(60)*. 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 the 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 subjects with normal glucose tolerance *(61)*. Insulin resistance improved in the acarbose group; however, BP declined equally in the two groups.

Although mostly limited to studies conducted in adults, these data suggest that many of the agents used to improve insulin sensitivity in patients with the MS and/or T2DM may have additional benefits in lowering BP. Further studies conducted in the young might provide a clearer picture of the effects of these agents on cardiovascular risk. At any rate, since the data are not consistent, 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 the desired 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 on the long-term effects of antihypertensive medications on growth and development, which add further uncertainty to the decision to initiate drug treatment. However, since accelerated cardiovascular disease occurs commonly in adult patients with the MS or T2DM, there is added impetus for starting drug therapy in the young.

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 1)
- Symptomatic hypertension
- Secondary hypertension

- Hypertensive target-organ damage
- Diabetes (types 1 and 2)
- Persistent hypertension despite nonpharmacologic measures.

Thus far, although it might seem reasonable to add the presumptive diagnosis of the MS as an additional indication for initiating drug therapy, no consensus organization has yet endorsed this, probably because of the difficulties defining the MS in pediatrics as discussed earlier. At the very least, children and adolescents with the MS and BP above the prehypertensive range who do not comply with or respond to a reasonable (6–12-month) trial of nonpharmacologic measures should probably be prescribed antihypertensive medications due to the likely risk of progression of the MS to frank diabetes, and because of 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 Chapter 31, so the following discussion will be limited to specific aspects pertinent to the MS and T2DM. One of the general principles of treatment of hypertension that is important to highlight here 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, necessitate the use of specific drug classes. Included in the 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 might depend upon the presence or absence of microalbuminuria, in which case an agent affecting the renin–angiotensin system would be favored *(62)*. Unfortunately, a similar evidence base is lacking for pediatric patients, as studies including subjects with comorbid conditions have not been conducted in the young.

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 drug's effect 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 individuals with impaired glucose tolerance and/or frank diabetes *(63,64)*. Alpha-blockers lower triglyceride and free fatty acid levels, and have no effect on total, high-density, or low-density cholesterol *(64)*, 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 *(65)*.

Calcium channel blockers have also been demonstrated to have beneficial effects on insulin sensitivity in patients with essential HTN *(66,67)*, so by extension would be appropriate for use in individuals with the MS. Even more encouraging is blockade of the renin–angiotensin system 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 *(68,69)*. Some of the newer ARBs appear to activate PPAR-γ, producing the beneficial effects of the thiazolidinediones without the weight gain and other adverse effects sometimes seen with those agents *(70)*. Therefore, many authors recommend ACE inhibitors and ARBs as the first-line agents for treatment of

HTN in patients with the MS *(71)*. The well-known activation of the renin–angiotensin system in obesity *(72)* would provide additional rationale for use of ACE inhibitors in children and adolescents with the MS or T2DM.

In contrast to the above, diuretics and beta-adrenergic blockers are usually thought to have "diabetogenic" potential *(73)* and might therefore be avoided as initial agents in treating HTN in patients with coexisting MS *(74)*. This position is supported by recent analysis of data from the ALLHAT study *(75)* that demonstrated a greater incidence of new-onset diabetes in the group treated with chlorthalidone compared to those treated with amlodipine or lisinopril *(76)*. However, this 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 beta-blocker is thought to be particularly diabetogenic *(77)*. 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 *(71)*.

Finally, adherence to prescribed therapy is another important issue that should be considered in the treatment of HTN because most patients have so few symptoms. In adolescents, this is particularly difficult because they often do not like to remember to take their medications and do not like to be perceived as different from their peers. If BP control can be achieved with a single drug that is taken once a day, this will improve the likelihood of compliance with taking the medication and should be taken into consideration when the initial agent is chosen. Adverse effects of the chosen agent should also be considered. Some classes of antihypertensive agents, particularly newer ones such as ACEIs and ARBs, have a lower incidence of adverse effects *(78)* and may be preferable when compliance is a concern. There are also combination preparations available that can improve compliance when more than one agent is needed to achieve the desired goal BP *(79)*. Early institution of combination therapy in treating hypertensive patients with T2DM has been advocated and appears to be supported by several recent clinical trials in adults *(80)*.

Goals of Therapy

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)*. This recommendation is gain based upon the results of large-scale clinical trials involving thousands of patients. Lacking large-scale trials in pediatric hypertension, the 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)*. By extension, the 90th percentile should probably be the target BP for 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.

SUMMARY

The increasing prevalence of obesity in children and adolescents is unfortunately being 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, signs

of insulin resistance are common and its consequences, most notably HTN, are readily detectable. 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 lifestyle modifications, as these measures have been proven effective in reducing BP and also in preventing progression to full-blown T2DM. Some oral hypoglycemic agents appear to have BP-lowering effects in adults, but pediatric data are lacking. When antihypertensive drugs are necessary, 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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19 Primary Hypertension

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Contents

INTRODUCTION

Pickering stated, "The relationship between arterial pressure and mortality is quantitative, the higher the pressure the worse the prognosis" *(1)*. Primary hypertension (HTN), which affects almost 20% of adults and is a major public health issue, is believed to have its antecedents during childhood. 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.

DEFINITIONS AND TECHNIQUES

HTN in children, unlike in adults, does not affect a large percentage of the pediatric population. Due to this, most of the data on HTN in children are from tertiary centers reporting a preponderance of secondary HTN. As reviewed by Flynn *(2)*, examination of this data shows shift toward higher reported prevalence (up to 50%) of primary HTN in children. Criteria for making a diagnosis of primary HTN are summarized in Table 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

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_19
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Table 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

or

➢ Ambulatory blood pressure measurements over a 24-h period that exceed the 95th percentile for age-matched controls (lack of diastolic HTN and normal dipping on ABPM are more consistent with primary HTN)

and

➢ 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; fundoscopic changes, cardiac enlargement by electrocardiogram and/or echocardiogram (suggestive of long standing HTN)

nomograms for BP in children are those reported by the Fourth Task Force Report on Blood Pressure in Children and Adolescents *(3)*. According to the recommendations of the Fourth Task Force Report, pediatric HTN is now categorized into pre-HTN (SBP or DBP between 90th and 95th percentile or greater than 120/80), stage 1 HTN (SBP or DBP $\leq$ 95th–99th percentile plus 5 mmHg), and stage 2 HTN (SBP>99th percentile plus 5 mmHg). Based on these recommendations, primary HTN in children is usually mild or stage 1 HTN and is often associated with a family history of HTN or 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. HTN definition is an arbitrary division in the continuum of BP, 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 occurs. As of this writing, there are no data that adequately define this in children. Not everyone agrees with the current definition because only the first BP reading was used to define normal values for the 83,000 children included in the BP nomograms for children and adolescents *(3,4)*. It is noteworthy that a comparison of normal BP readings reported by 10 different investigators reveals that the highest and lowest (50th and 95th) percentile values for boys differ by 20 mmHg *(5)*. Other confounding factors in BP measurement in children include the cuff size, number of measurements, type of instruments used, patient position (supine or sitting), and the choice of sound (Korotkoff (K) 4 versus K 5) used for defining diastolic BP *(3)*. Ambulatory blood pressure monitoring (ABPM) has been used increasingly in the past decade to diagnose HTN, define diurnal BP variability in normal and hypertensive populations (including children) *(6)*, and evaluate therapy. ABPM is essential for diagnosing white-coat

HTN and may sometimes help to distinguish primary versus secondary HTN in children. Nocturnal dipping during ABPM is believed to reflect decreased sympathetic nervous system activity. BP load and non-dipping have been associated with end-organ changes and possibly higher risk for secondary HTN *(7)*. Masked HTN is a condition in which subjects classified as normotensive by conventional office measurement are hypertensive with ABPM or self-measurement. Lurbe et al. have estimated the prevalence of masked HTN at 9% in children/adolescents with persistence in 50% of these patients *(8)*. Lurbe et al. *(8)* and Stabouli et al. *(9)* have reported progression to sustained hypertension and hypertensive end-organ damage (increased left ventricular mass index) in patients with masked hypertension. These findings make a case for treatment of patients with masked HTN to prevent cardiovascular complications of hypertension.

PATHOGENESIS OF HTN *(10–12)*

An overview of the steps involved in the generation and a persistent phase of HTN (Tables 2 and 3) serves as a basis upon which risk factors, clinical evaluation, and treatment of primary HTN in children are better understood. HTN occurs when the sum of cardiac output (CO) and total peripheral resistance (TPR) increases. Each parameter is influenced by other factors, which may increase or decrease the relative contribution of volume and/or vasoconstrictor components of the BP formula. The factors involved in increasing BP during the generation and maintenance phases 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 *(13)*. 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 *(14)*. 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 proposed mechanisms for these changes include (1) auto-regulation, an intrinsic feature of vasculature characterized by increased flow-induced vasoconstriction, and (2) vascular structural changes including hypertrophy and eventually fibrosis. According to Folkow hypothesis *(15)*, peripheral resistance increase

Table 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) × resistance (arteriolar functional contraction + vessel anatomical changes), e.g., BP = Flow × Resistance
5. HTN = a net increase in CO and/or increased peripheral resistance

Table 3
Factors Involved in the Generation and/or Persistence of HTN

Cardiac output
Preload
Increased fluid volume
➢ Renal sodium retention: genetic factors, decreased glomerular filtration surface, and renin aldosterone effect
➢ Excess sodium intake
Volume redistribution
➢ Sympathetic nervous system overactivity: genetic factors, stress (personal and environmental), and renin angiotensin excess
Contractility
➢ Sympathetic nervous system overactivity and genetic factors
Total peripheral resistance
Functional vasoconstriction
➢ Renin angiotensin excess, sympathetic nervous system overactivity, genetic influence on cell membrane function, and endothelins
Structural constriction
➢ Folkow hypothesis, renin–angiotensin excess, sympathetic nervous system overactivity, endothelins, and hyperinsulinemia

in hypertension of any etiology is most likely related to increased vascular mass. This amplifies the extent of contraction resulting from vasoactive stimuli and, thus, markedly increases resistance to blood flow and systemic blood pressure in the vessels of hypertensive patients. There is controversy over the primary mechanisms involved, as they may operate independently or collectively. 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.

Electrolytes

In chronically hypertensive individuals it is hypothesized that the normal relationship between BP and natriuresis is reset at a higher level, which may be genetically determined. Abundant evidence exists to support a major role of sodium in the etiology of essential hypertension (Table 4). Salt-sensitive individuals are estimated at 25–50% of the adult population and in them BP changes correlate with an increase or decrease in salt intake. 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 *(16)*, nephron heterogeneity *(17)*, and nonmodulation that involves abnormal adrenal and renal responses to angiotensin (ANG) II infusions *(18)*. Intake of other ions like calcium and potassium also influences BP. Increased potassium intake by Dutch children over a 7-year period was associated with a mean yearly increase in systolic BP of 1.4 mmHg, while children ingesting a low potassium intake experienced a systolic BP raise of 2.4 mmHg per year *(19)*. Low calcium intake or its

Table 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
- ➢ Decreases in salt intake in people with borderline high BP may prevent the onset of HTN
- ➢ The time and the quantity of sodium administration to rats genetically predisposed to HTN determine the onset and the 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

increased excretion can lead to hyperparathyroidism, which presumably causes hypertension by altering contractility in vascular smooth muscle *(20)*.

Hormones (10,11)

RAAS (Renin–Angiotensin–Aldosterone System): The renin–angiotensin–*aldosterone* system (RAAS) influences both elements of the BP formula. ANG II binding to AT1 receptors in vascular smooth muscle increases contractility as well as sensitivity to catecholamines. 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. Studies have shown that aldosterone receptor antagonist improves endothelial dysfunction, increases NO, and prevents nephrosclerosis.

Catecholamines: Sympathetic nervous system (SNS) activity can function as an initiator and as a secondary contributing factor. 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 the stimulation of presynaptic β2 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. 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 rats to the D1 receptor. One D1 and D2 receptor polymorphism has been associated with HTN; however, the mechanism is unclear. The systemic affects of the *natriuretic peptides (A, B, and C)* result in reduction of both preload and afterload, especially in conditions with intravascular volume expansion. Mutations in ANP genes have been described in hypertensive patients and other cardiovascular disease.

Endothelial-Derived Hormones: Endothelin (ET-1) signals through ET-A and ET-B receptor subtypes. The balance between the vasoconstrictor effects of ET-A and vasodilator effects of ET-B determines the overall effects of ET-1. Nitrous oxide (NO), synthesized by the endothelium form L-arginine, is predominantly a vasodilator. The balance between NO and endothelium-derived vasodilators and the SNS maintains the vascular tone. Neuronal NO has also been shown to influence the autonomic regulation of BP. Other hormones linked to blood pressure regulation include adenosine (endothelium derived), triiodothyronine, and adrenomedullin peptide.

Genetic Influences

The theory of impaired genetic homeostasis postulates *(21)* 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. Low birth weight, increased placental weight, and HTN *(22)* result in a phenotype that is insulin resistant and hypertensive and possibly associated with abnormalities in 11β-hydroxysteroid dehydrogenase activity *(23)*. Synchronicity, a process by which growth spurts are associated with increases in BP, may be accelerated in genetically prone hypertensive individuals *(24)*. Allometric dysfunction, a process by which somatic and renal growth fail to match each other, might lead to HTN if environmental factors enable excessive non-genetically determined growth to occur *(25)*. 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 *(26)*. 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 *(27)*.

PREDICTORS OF PRIMARY HTN

Tracking (12) refers to the pattern of repeated BP measurements over a period of time. The clinical importance of tracking in children with annual BP over the age of 3 years is related to the ability to predict BP status later in childhood and adulthood. Children who are hypertensive are more likely to remain hypertensive throughout childhood and as adults, particularly in the presence of a family history of HTN, increased body weight, or increased left ventricular mass *(28,29)*. The Muscatine study *(30)* has demonstrated that in children with two or more systolic or diastolic BP readings above the 90th percentile or any SBP reading above the 90th percentile, 24–25% of adult readings were above the 90th percentile while in children with three BP readings less than the 90th percentile, 6–7% of

adult readings were above the 90th percentile. A recent meta-analysis of published studies on BP tracking confirms the presence of childhood BP tracking into adulthood across diverse populations, with stronger association seen with older ages *(31)*.

RISK FACTORS INVOLVED IN CHILDHOOD PRIMARY HTN *(10–12)*

Age and Gender

Children have lower BP levels in comparison to adults, but the levels progressively increase as the child ages, 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 post-pubertal group. The prevalence of HTN and pre-HTN is greater in boys than in girls *(32)*. Also, in girls BP rises rapidly between 6 and 11 years of age, than it does from 12 to 17 years, while the opposite is seen in boys *(10)*.

Race and Ethnicity

The prevalence of primary HTN is clearly influenced by race and ethnicity *(33)*. 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. Muntner et al. *(34)* and Din-Dzietham et al. *(35)* have also reported on the prevalence of higher BP levels in minority youth. These differences are most likely quantitative *(36)* 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 *(37)*. Blacks have higher sleep and less dipping in their nighttime ABPM values than age-matched whites *(38)*. 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 *(39)*. Possible factors include increased salt sensitivity, activity of the RAAS (genetic polymorphism), and transforming growth factor β. Several studies have reported that blacks have a poorer response to both angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers. The addition of a diuretic to these agents improves the response.

Renin Profiling

Laragh et al. have proposed that patients with primary HTN can be divided into three groups: normo, hyper, and hypo reninemic based on renin profiling, e.g., the comparison of plasma renin activity (PRA) to sodium excretion *(40)*. This group concluded that high-renin primary HTN patients are at greater risk for vasoocclusive events such as stroke, infarction, and renal failure, while those with low-renin primary HTN are volume over-expanded 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% *(41)*. There are 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 *(42)*. 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 *(43)*. Flynn et al. have reported that high PRA is associated with higher BP load and correlates positively with diastolic BP, but not with systolic BP *(44)*.

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 *(45)*. 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 *(46)*. 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 *(47)*. Increased urinary excretion of cortisol and endothelin in adolescents with WCH identifies a group with distinct metabolic abnormalities *(48)*. 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) *(49)* and one that remains normotensive outside the clinical setting.

Fetal Development

Baker first proposed that HTN in adult life is associated with retarded fetal growth and this relationship becomes stronger as the patient ages *(22)*. 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 *(50)*, 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 *(51)*. The impaired nephron function eventually leads to HTN.

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. Prevalence studies, including tracking studies of weight change and BP in young adults *(52)*, 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 *(53)*. The Muscatine Study showed that changes in ponderosity over 11 years correlated directly with BP changes *(30)*. Obesity is associated with "metabolic syndrome," which is characterized by insulin resistance, an atherogenic dyslipidemia, activation of the sympathetic nervous system, and an increased tendency for thrombosis—suggest using a reference for metabolic syndrome. Other suggested mechanisms of obesity-related HTN include hyperinsulinemia, hyperproinsulinemia, renal sodium retention, increased sympathetic activity, increased plasma volume, increased levels of dehydroepiandrosterone *(54)*, and increased CO (for further discussion, see Chapter 17).

Increased plasma aldosterone activity in obese adolescents correlates with increases in their mean BP; the BP level falls when weight loss occurs *(55)*.

Salt Intake (Table 4)

The average sodium intake in American diet has increased almost fivefold to approximately 3400 mg/day, a level sufficiently high enough to enable high-BP expression in salt-sensitive individuals *(56)*. Also, epidemiologic studies have shown that BP levels are higher in societies with high salt intake *(10)*. Experimental studies 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 mmHg lower BP after 6 months *(57)*. Even though this difference did not persist a few years later, it is still possible that a lifelong effect may be seen. The findings of the Intersalt study *(58)* and PREMIER study *(59)* challenge the recommendations regarding the DASH (dietary approaches to stop HTN) diet as central component of combined lifestyle modification for HTN treatment. Furthermore, the DASH study recommendations are limited due to a follow-up of only 30 days, and the association between sodium intake and risk from adverse events has not been demonstrated in non-obese subjects. In children, this issue is further complicated as sodium is essential for normal growth and development.

Exercise

Exercise (aerobic and static) transiently increases BP. 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. The BP response of hypertensive adolescents to exercise is similar to that of normotensive adolescents, but starts and finishes at higher levels *(60)*. 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 *(61)*.

Lipids and Cigarette Smoking

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 *(62)*. 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 non-coronary artery disease events revealed fatty aortic streaks in 61%, coronary artery fibrous streaks and/or plaques in 85%, and raised plaques in 25% *(62)*. 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.

Genetics

Approximately 60–70% of HTN in families can be attributed to genetic factors and the remainder to environmental factors *(63)*. Comparison of dizygotic with monozygotic

twins supports a hereditary estimate of 0.72 and 0.28 for DBP and SBP, respectively *(64)* (for further discussion, see Chapter 14). The observations that dizygotic correlations are higher than other first-degree relatives support a role for shared environmental cause *(65)*. Attempts to identify specific candidate genes involved in primary HTN have yielded inconsistent results. Such differences may reflect environmental factors, the influence of other genes, evolutionary diversion (race and ethnicity), and study design and/or technical issues. At least 25–30 genes have been suggested as contributors to the hypertensive process (Table 5 *(66)*). ACE/ID polymorphisms are believed to play a major role in both the onset of primary HTN and its treatment. Individuals homozygotic for the D allele have higher levels of ACE. The DD genotype has been associated in some, but not all, studies with a reduced antiproteinuric effect to ACE inhibitor antihypertensive agents. In such patients, AT1 receptor blockades may improve BP response and retard progression of renal disease *(67)*. The genes controlling plasma angiotensinogen (AGT) clearly influence BP while those involved in ACE production do not *(68)*. The Gly460Trp variant of the α-adducin gene has been associated with HTN more in blacks *(69)* than in whites. A number of renal transplantation experiments, between genetic strains of primary HTN and normotensive rats, as well as

Table 5
Partial Listing of Chromosomes, Genes, and Flanking Markers Involved in HTN

Chromosome 5q31-q34 (marker bordering region D5S2093), ADRB2 allele Arg16Gly

* β-adrenoceptor-G-protein system: chromosome 20q13.2, gene GNAS1 exon 5, allele Fok1.chromosome 12p13, gene GNB3, exon 10. Allele C825T

α-adducin

* Chromosome 4p, gene alpha adducin. Allele Gly460Trp
* Catecholamine synthetic enzymes: (a) dopamine-β-hydroxylase gene, (b) phenylethanolamine *N*-methyltransferase gene, and (c) tyrosine hydroxylase gene
* Chromosome 18q *(74)*
* Genomic array identified genes: (a) 2p22.1-2p21, 5p33.3-5q34, 6q23.1-6q24.1, 15q23.1-15q26.1; (b) chromosome 11q, marker D11S934; and (c) chromosome 15q, marker D158203
* Lipoprotein metabolism

Chromosome 8p22, gene lipoprotein lipase

* Chromosome 2p24, gene apolipoprotein, and allele β 3′ promoter hypervariable region
* Miscellaneous genes: (a) glucagon receptor, (b) glucocorticoid receptor, (c) prostacyclin synthase, and (d) transforming growth factor β (TGF-β) 1 gene
* Renal kallikrein-kinin system: (a) chromosome 19q13 and (b) gene tissue kallikrein (KLK1) 5′ proximal promoter
* Renin–angiotensin–aldosterone system: (a) angiotensinogen gene alleles M235T, A-6G, and A-20C and (b) ACE locus deletion/insertion (D/I) polymorphism intron 16
* Aldosterone synthase (CYP11B2 on chromosome 8p21) alleles –344T
* Epithelial sodium channel (ENaC): subunit β T594M mutation (nearby β gene 16p12.3) *(75)*

Adapted unless otherwise stated from *(66)*.

human transplantation *(70)*, support the concept that the genetic composition of the kidney plays a role in determining HTN.

Stress

Stress of all types can increase BP. Poverty, socio-cultural factors, racial issues, and migrations 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 *(71)*. Type A behavior is associated with increases in SBP, but not in DBP *(72)*. Three models of psychosocial stress that might explain the genesis of primary HTN are the Defense Defeat Model, Demand Control, and Lifestyle Incongruity Index *(73)*. These models deal with issues such as fight flight, control, aggression, depression, subordination, the relationship between psychologic demand factored by the available latitude of decision-making, and differences between occupational and social class and achievement versus accomplishment.

CONCLUSION

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 to be evaluated for any underlying secondary causes. An understanding of the pathophysiology, genetic mechanisms underlying primary HTN in children, holds the promise of modification of behavioral traits, designer drug therapy, and improved interpretation of gene expression (thereby likely gene therapy in future). This will help in addressing both the public health issues and individual needs of hypertensive children and adults.

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20 Secondary Forms of Hypertension

Kjell Tullus, MD, PhD, FRCPCH

Contents

INTRODUCTION

In most studies, hypertension in children has been secondary to an identifiable cause in a large majority of those studied *(1,2)*. This has changed during the relatively recent epidemic of childhood obesity, where primary hypertension in many centers now is the most common cause form of hypertension *(3)*. In adults primary hypertension is the dominating diagnosis. This chapter will discuss those cases where a cause for the hypertension has been possible to identify. It is quite possible that in the future some children that presently are diagnosed with primary or essential hypertension will be found to have an underlying diagnosis.

The causes of secondary hypertension vary considerably with the age of the child. They can be defined as acute forms of hypertension related to an acute episode of a disease or its treatment, or chronic secondary hypertension. The blood pressure in the former children often normalizes when the acute disease is resolved while in latter often the problem persists for many years, even indefinitely. Of course, some children with acute hypertension will develop a more sustained or chronic disease.

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_20
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ACUTE SECONDARY HYPERTENSION

There are numerous causes for acute transiently increased BP (Table 1), the most common being acute renal failure or acute glomerulonephritis (GN). Two common diagnoses in children are hemolytic uremic syndrome (HUS) and post-streptococcal GN. Salt and water retention is a prime mechanism behind this hypertension. Many cases of GN and in particular diagnoses causing impaired blood flow by narrowing of blood vessels, as in vasculitides or HUS, may also have a renin-mediated process. Salt and water overload of other causes (e.g., iatrogenic) can also cause hypertension.

Paradoxical hypertension can be seen in children with intravascular volume depletion as such as in the acute phase of nephrotic syndrome *(4)*. This form of hypertension is caused

Table 1
Causes of Acute Transient Hypertension

Renal parenchymal disease
Acute glomerulonephritis
Acute tubulointerstitial nephritis
Hemolytic uremic syndrome
Acute renal failure of any cause
Acute urinary tract obstruction
Salt and water overload
With acute renal failure
Iatrogenic—giving too much salt and water
Iatrogenic—salt retaining hormone treatments
Vascular
Renal vein and renal artery thrombosis
Embolic disease
Vasculitis
Renal compression—tumor, post-trauma, or surgery
Neurological
Raised intracranial pressure
Guillain–Barré
Poliomyelitis
Dysautonomia
Drug mediated
Oral contraceptives
Sympathomimetic drugs
Erythropoietin
Drugs for hyperactivity in ADHD
Illicit drugs e.g. cocaine and amphetamine
Diet mediated
Alcohol
Licorice

by renin release to produce vasoconstriction, and normalizes after volume repletion. Several neurological conditions can cause hypertension, in particular increased intracranial pressure but also conditions such as Guillain–Barré syndrome and poliomyelitis *(5,6)*.

Many drugs, including not only illicit drugs such as cocaine, but also prescribed agents such as corticosteroids, can cause severe hypertension (Table 1) *(7)*.

CHRONIC SECONDARY HYPERTENSION

The causes of chronic secondary hypertension are quite different in different age groups. In neonates the most common are malformations in the kidney or coarctation of the aorta (CoA) (Table 2) *(8)*. Problems related to prematurity and its treatment, including chronic lung disease and thrombotic events of the renal arteries or veins, are also important. A more thorough discussion of neonatal hypertension is found in Chapter 21. In older infants renal malformations and renovascular disease (RVD) become the predominant diagnoses (Table 3).

Table 2
Common Causes of Hypertension in Neonates

Renal artery or vein thrombosis due to umbilical catheter
Renal venous thrombosis
Congenital renal malformations
Coarctation
Chronic lung disease
Post-ECMO
Midaortic syndrome and/or renal artery stenosis

Table 3
Common Causes of Hypertension in Infants

Renal parenchymal disease
Renovascular disease
Medication
Chronic lung disease

An overview of the most common causes of hypertension seen at Great Ormond Street Hospital for Children is given in Table 4. Such a list will, however, vary from hospital to hospital and also from time period to time period but gives a general impression of the most common diagnoses. I will here discuss the most important causes of secondary hypertension in more detail (Table 5).

Table 4
Causes of Sustained Hypertension at Great Ormond Street Hospital for Children

Renal scarring	36%
Glomerulonephritis	23%
Renovascular hypertension	10%
Coarctation	9%
Polycystic kidneys	6%
Post-HUS	4%
Idiopathic	3.5%
Catecholamine excess	3%
Wilms' tumors	2.5%
Miscellaneous	4.5%

Table 5
Causes of Chronic Hypertension

Parenchymal renal disease
CAKUT
Chronic glomerulonephritis
Polycystic kidney diseases
Other parenchymal kidney diseases
After an acute kidney disease such as HUS
Renovascular disease
Fibromuscular dysplasia
Sometimes with midaortic syndrome
Chronic renal failure
Often worsening with worsening renal function
Tumors
Coarctation of aorta
Pulmonary
Chronic lung disease of the newborn
Endocrine
Catecholamine excess
Pheochromocytoma
Paraganglioma
Neuroblastoma
Corticosteroid excess
Iatrogenic
Cushing's disease
Conn's syndrome
Monogenic disorders
See Chapter 6

RENAL PARENCHYMAL DISEASES

Twenty-five percent of children with chronic kidney disease are either hypertensive or prehypertensive *(9)*. Several parenchymal kidney diseases in particular have hypertension as an important symptom. These include CAKUT (congenital abnormalities of the kidneys and the urinary tract), chronic glomerulonephritides and polycystic kidney diseases. Volume expansion due to reduced sodium excretion and increased activity in the renin–angiotensin axis are two important mechanisms for this hypertension. Others are reduced production of vasodilators and activation of the adrenergic system *(10)*.

CAKUT

CAKUT represents a heterogeneous group of children with congenital damage to the renal parenchyma. This diagnosis is the most common in children with renal impairment. Many different diagnostic terms are used for similar conditions emphasizing different diagnostic or etiological aspects. Some stem from a proposed etiology such as reflux nephropathy or obstructive nephropathy, others are based on a pathological diagnosis such as hypoplastic or dysplastic kidneys and "chronic pyelonephritis" while others are based on the radiological appearance, for example, multicystic dysplastic kidneys. A further commonly used term is scarred kidneys, implying secondary kidney damage due to a process such as acute pyelonephritis. These diagnostic labels are often neither in clinical practice nor in most scientific studies used with a clear distinction between them. It is often difficult to separate congenital dysplastic kidneys from kidneys harmed from acute infections and no consensus on how to best define these diagnoses exists.

These diagnostic difficulties most likely explain the great variation in the reported frequency of high blood pressure in different studies in these children. A population-based study of all children with renal scarring detected during a 10 year period and followed for a mean of 17 years found similar 24-h blood pressure in the children with renal scars compared to those without *(11)*. This contrasts markedly to other studies in more selected populations, such as that from Great Ormond Street Hospital for Children, where renal scarring was the most common cause (36%) for hypertension and up to 20% all children with a renal scar were estimated to get high blood pressure *(12)*. A study from eastern Europe showed that children with more extensive kidney scars on their DMSA scan had higher BP than children with no scars or less extensive scars *(13)*.

Many children with congenital malformations have tubular dysfunction, with impaired reabsorption of sodium, and inability to concentrate their urine. They do therefore often loose both salt and water, which explains why a majority of these children have normal or low blood pressure. Please also see Chapter 22.

Chronic Glomerulonephritides

Children with long-standing ongoing inflammation in their kidneys frequently have high blood pressure as one major symptom. The cause of this high blood pressure is multifactorial, with water retention, vascular constriction, and renin release as important components. Children with chronic GN resulting in chronic renal impairment frequently have persistent proteinuria, which has been associated with a greater likelihood of having hypertension compared to children without proteinuric renal disease *(9)*.

Autosomal Recessive Polycystic Kidney Disease and Autosomal Dominant Polycystic Kidney Disease

Children with polycystic kidneys often have high blood pressure as an important symptom even before they develop impaired kidney function. In autosomal recessive polycystic kidney disease (ARPKD), the high blood pressure is often evident already during the first month of life. Also children with autosomal dominant polycystic kidney disease (ADPKD) do often display hypertension long before any signs of impairment of kidney function *(14,15)* (Fig. 1). The mechanisms behind the hypertension are debated, with activation of the renin–angiotensin system still most likely being of major importance *(16)*.

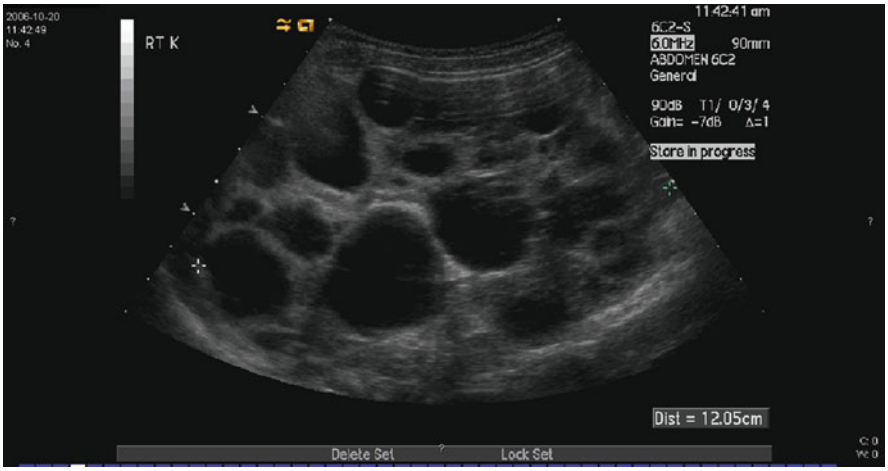

Fig. 1. Renal ultrasound of the right kidney of a 1-month-old boy with ADPKD and severe hypertension.

Aggressive treatment of the blood pressure, in particular with agents blocking the RAS, is hoped to be able to slow down the progression of renal failure, but no clear evidence exists to support that notion *(17)*.

Hypertension After Severe Acute Renal Diseases

Children with acute kidney diseases such as HUS often suffer from very difficult-to-treat high blood pressure during the acute phase of the disease. In some of these children, in particular those with atypical HUS, the high blood pressure persists also after the acute episode, and management of the blood pressure remains a very important issue *(18)*. This is particularly true as the pressure stress on the endothelium caused by the hypertension might trigger further relapses of the HUS. Ambulatory blood pressure recordings have shown that also a high proportion of children who have recovered from severe HUS caused by Shiga toxin-producing *Escherichia coli* have persistent hypertension *(19)*.

Hypertension Associated with Severe Renal Failure

Children in end-stage renal failure, children on dialysis, or children who had a kidney transplant are frequently hypertensive. For a thorough discussion of hypertension in these conditions, please see Chapter 23.

RENOVASCULAR DISEASE

RVD causes some 10% of hypertension in children, and has been extensively reviewed elsewhere *(20)*. It is important to diagnose as it is potentially curable with interventional treatment. The extent of RVD ranges from the with narrowing of only one renal artery to the large group of children with extensive involvements of their vascular tree *(21)*. In 53–78% of cases there is involvement of both renal arteries and in a third there is also intrarenal small artery disease *(22,23)*. A large group (20–48%) of these children have associated midaortic syndrome (MAS) (Fig. 2) *(24,25)*, that is, narrowing of the abdominal aorta. Involvement of the celiac axis and the superior and inferior mesenteric arteries occurs in 53% of cases and cerebral artery disease is also found in a large proportion.

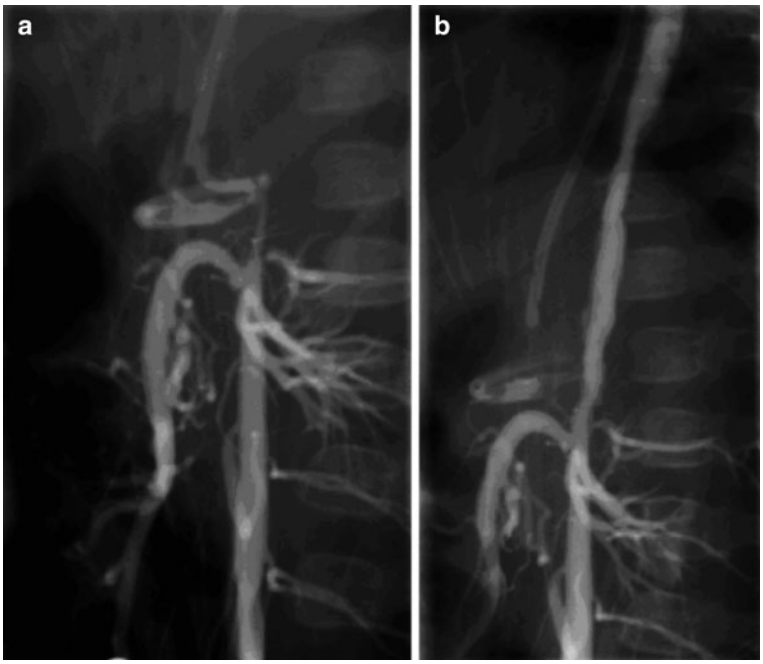

Fig. 2. Severe midaortic syndrome seen before (**a**) and after (**b**) treatment with angioplasty.

There are many causes of RVD in children and they are quite different than those in adults where atherosclerotic disease is the predominant diagnosis. In children a developmental abnormality of the vessel wall is the most common diagnosis *(26,27)*. This is often called fibromuscular dysplasia, but it is uncommon to have pathological confirmation of the diagnosis. The typical pattern with so-called beading on angiography is also often not present (Fig. 3a). Certain syndromes, in particular neurofibromatosis type 1 and William syndrome, are overrepresented among children with RVD even if most children with these syndromes do not have RVD *(28–30)*. Children with vasculitis can also develop clinically significant narrowing of their renal arteries. In some reports, Takayasu's disease is an important cause while we at Great Ormond Street Hospital in London see very few of those cases *(31,32)*. Tumors, radiation, and trauma can also cause significant RVD.

RVD is in a large proportion of children 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.

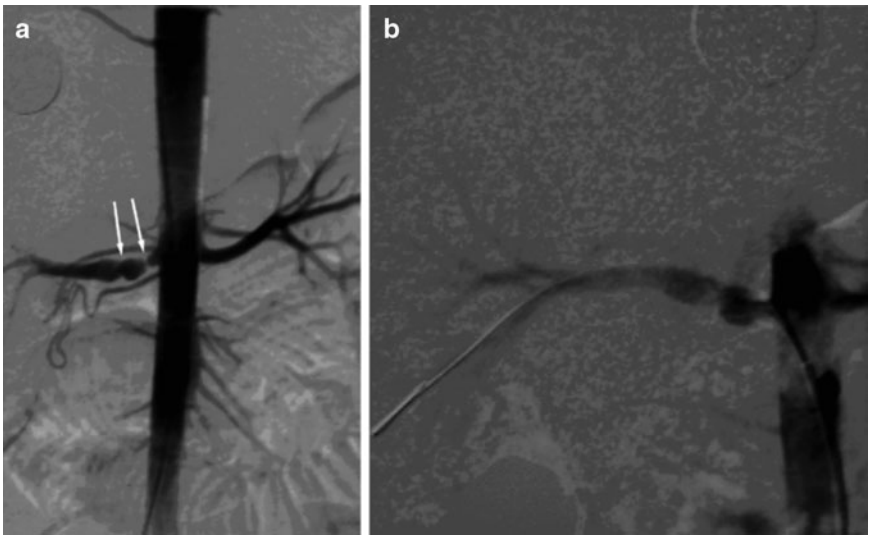

Fig. 3. (**a**) Typical beaded appearance of a renal artery with severe stenosis. (**b**) After treatment with angioplasty.

The hypertension in RVD is caused by a combination of renin-mediated mechanisms and sodium-related volume expansion. Increased sympathetic nervous system activity can also play a role.

Children with RVH do often present with very high BP; it is not uncommon for patients to have systolic blood pressure well above 200 mmHg, with maximum blood pressure even reaching 300 mmHg in some cases. The clinical presentation of these children is very variable. Many children (26–70%) are completely asymptomatic, and are diagnosed as a chance finding, but some can present with severe, potentially life-threatening cerebral or cardiac symptoms such as stroke and heart failure *(23,33–35)*.

The most reliable way to diagnose RVD is with digital subtraction angiography (DSA), which is the only method that can reliably define the extent of the RVD *(21,36)*. Angiography is, however, invasive and general anesthesia is needed in most cases. Other less invasive investigations are therefore used to help to define the group of children that need to undergo DSA. These investigations include those commonly used for all children with high BP, including routine laboratory studies. For example, elevated plasma renin activity or aldosterone, or low to low normal serum potassium can often be seen in children with RVD, but are not always present. Thus, a high index of suspicion needs to be maintained when investigating children with otherwise unexplained severe hypertension.

Renal Doppler ultrasound may in some cases be very helpful in detecting RVD but is in a many cases unable to detect the renal artery stenosis *(37–39)*. The resistance index has been used to measure blood flow in kidneys but the sensitivity is too low for it to rule a need for angiography *(40)*. Pre- and post-captopril renal scintigraphy has been widely used to screen for RVD, based on the concept of reduced blood flow to the kidney or part of the kidney after administration of the angiotensin-converting enzyme inhibitor (ACEi) *(41)* can be seen as reduced relative function of one kidney or as a new uptake defect in on or both

kidneys. The sensitivity (50–73%) of this investigation has, however, not been shown to be good enough to make the use of this procedure useful in clinical practice *(38,42–46)*.

Newer imaging modalities such as computed tomography angiography (CTA) and magnetic resonance angiography (MRA) can be helpful in detecting and monitoring vascular lesions. 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 *(20,38,47,48)*. 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 *(49)*. As children have smaller blood vessels, this might be a bigger problem in the younger population. In our own experience, we have seen that CTA and MRA can both over- and underdiagnose RVD in children.

Measurement of renal vein renins is in many cases helpful in deciding how to treat a child with RVD *(50–52)*. 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 the main renal veins and their main branches in both kidneys. This information can be used in the defining which part of the kidney(s) that seems to produce increased levels of renin and thus to decide which of often several artery stenosis that should be given priority in the 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. Medicines are useful in most children with RVH and are often needed as adjunctive therapy in children who have successfully undergone surgery or angioplasty. It is important not to use an ACEi in these children as this very often can cause a major deterioration in the function of the affected kidney(s) *(53)*. This can in cases with unilateral renal artery stenosis only be monitored with renal scintigraphy as serum creatinine is not sensitive enough to detect deterioration of the function in one kidney.

With modern technology, angioplasty can cure or improve the blood pressure in at least 50% of children *(35,54,55)* (Fig. 3). The angioplastied artery has in many children a tendency to undergo restenosis. In some cases, a stent can be placed to keep the artery open *(35,56–58)* (Fig. 4). The lumen of some stents will with time narrow down. This can be due to intimal hyperplasia within the stent or due to thrombosis of the stent. In adult coronary arteries, stents coated with an anti-proliferative agent such as sirolimus have been used to reduce the occurrence of intimal hyperplasia. This does however seem to increase the risk of early thrombosis of the stents and no clear scientific opinion on which stent is preferred exists at the present time *(59)*.

Some children not amenable to angioplasty can be treated with ethanol ablation of a part of a kidney *(52,60)*. This is particularly useful in polar arteries supplying only a small part of one kidney. Surgery should only be used in children where angioplasty has not achieved good enough blood pressure control. There are many different surgical options including nephrectomy of a kidney with very little function and different revascularization procedures. Nephrectomy is often very successful at curing the blood pressure in particular if there is unilateral disease *(61,62)*. We have occasionally seen kidneys that on a pretreatment DMSA scans demonstrated <10% function that after successful angioplasty or revascularization surgery have recovered up to 50% relative function (Tse personal communication). These kidneys may survive on collateral circulation that in ordinary circumstances does not result in meaningful kidney function, but the function can sometimes be recovered. We use the size of the affected kidney on ultrasound to decide when to try to recover function or to go directly to nephrectomy.

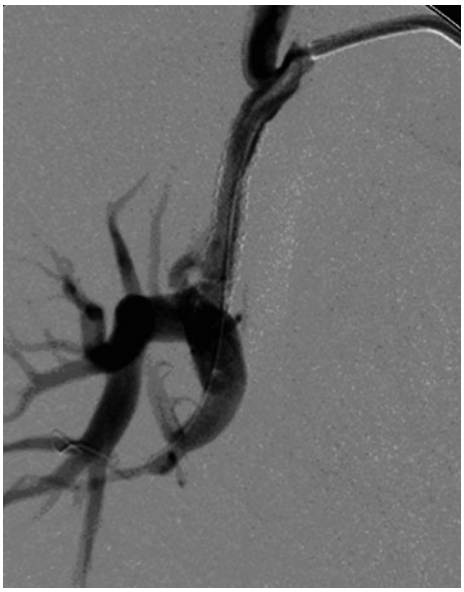

Fig. 4. Renal artery stented after angioplasty.

Revascularization surgery can be performed in several different ways: surgery on the renal arteries with autologous or synthetic grafts inserted or aortic reconstruction with or without a synthetic graft *(62–64)*. The autologous grafts can be the splenic or the gastroduodenal artery that is pulled to the kidney, part of the saphenous vein or internal iliac artery. Dacron is often used for the synthetic grafts (Fig. 5). The surgery on the renal arteries can sometimes be so complicated and time consuming that it needs to be done outside of the

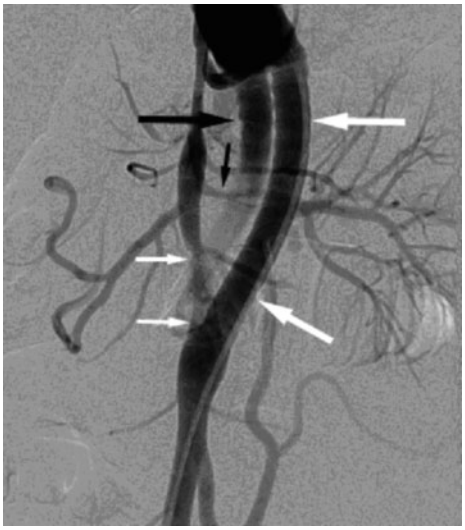

Fig. 5. A so-called trouser graft from upper aorta linking on to lower aorta (*big white arrow*) and left renal artery (*big black arrow*).

child with an ensuing autotransplantation. With complicated pathology such as bilateral stenosis and MAS, a so-called trouser graft can be used that goes from the aorta above the MAS down to the aorta below the MAS and one or both renal arteries.

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 in 90% of the children undergoing surgery *(61,65)*.

RENAL TUMORS

Different tumors can cause hypertension through two primary mechanisms: direct pressure on the renal blood vessels or aorta, or through hormones secreted from the tumor (see below). Wilms' tumors cause hypertension in a majority of cases, but also other more uncommon renal tumors such as reninomas and occasionally hamartomas can also cause HT *(66–68)*.

COARCTATION OF THE AORTA

CoA accounts for a few percent of children with high blood pressure. It is amenable to potentially curable surgical treatment and is therefore important to diagnose early *(69,70)*. CoA is mostly diagnosed in newborn children or infants but may be detected at later ages. 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 presurgery is renal hypoperfusion with increased renin–angiotensin activity. When hypertension persists postsurgery, it is most likely caused by both renin and sympathetic nervous system activities *(71–73)*.

The presenting symptoms are mostly detection of a murmur or raised blood pressure on measurement. The diagnosis is normally suspected clinically from the combination of higher blood pressures in the arms compared to the legs, the sometimes absent femoral pulses and the systolic ejection murmur that 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 *(69)*.

The optimal treatment for coarctation has with time become controversial *(74)*. 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 *(75)*. This is, however, particularly in smaller children quite controversial *(70)*.

Narrowing can occur also in other parts of the aorta. Typical is narrowing of the abdominal aorta. This was previously called abdominal coarctation but the modern preferred term is MAS. MAS is in most cases related to other vascular pathology and seems in children to fall into the same spectrum as RVD (see above).

The BP in children with CoA does mostly normalize postsurgery. However a significant proportion of children will still need some antihypertensive treatment also after the surgery. This risk seems to increase over several decades and is higher in children treated at an age of more than 1 year compared to children who were treated during their infancy *(72,76)*. This can be caused by reoccurrence of the stenosis but is in most cases not fully understood.

PULMONARY CAUSES

There is a well-known relation between chronic lung disease of prematurity and high blood pressure in neonates *(77,78)*. For details please see Chapter 21. The mechanisms behind this blood pressure are not fully understood but treatment with steroids can play a role. Chronic hypoxia has also been thought to be of importance.

ENDOCRINE

Endocrine causes of high blood pressure can mainly be divided into those that are caused by excess catecholamines or excess corticosteroids.

Catecholamine Excess

Catecholamine excess is a very important but rare cause of hypertension in childhood as it is amenable to curative surgery *(79,80)*. It is regarded to cause 1% or less of all childhood high blood pressure. The lesions can mostly be divided into pheochromocytoma (80%) and paraganglioma; and occasionally a neuroblastoma can produce catecholamines that cause high blood pressure *(81,82)*. Pheochromocytomas are tumors that arise from chromaffin cells in the adrenal medulla while paragangliomas arise from the sympathetic or the parasympathetic paraganglia. The parasympathetic paragangliomas are normally nonfunctioning.

Pheochromocytomas and paragangliomas are often familial and in some studies more than 50% related to a mutation in one of the *VHL* (von Hippel–Lindau type 2), *SDH* (succinate dehydrogenase; paraganglioma syndrome) B and D, *MEN2* (multiple endocrine neoplasia type 2), or *NF1* (neurofibromatosis type 1) genes *(79,83)*. All these are inherited in an autosomal dominant manner. The mechanism might be via impaired apoptosis of sympathetic neuronal precursor cells. A majority of these tumors are benign but a significant proportion are malignant. Histopathological evaluation after surgery is very important to confirm the diagnosis and to attempt to quantify the risk of malignancy and recurrence *(84)*. Certain mutations, in particular the SDHD, have a higher risk of malignancy *(85)*.

Children with pheochromocytomas can present in very different ways, most with some degree of hypertension that can be sustained (60–90%) or variable *(86,87)*. Other classical symptoms are those related to very high blood pressure or to the increased catecholamine levels such as headache, sweating, flushing, palpitation, syncope, blurred vision, tremor, panic attacks, and weight loss. In some reports, only 60% of children with pheochromocytoma had high blood pressure *(88)*.

The diagnosis is based on increased urinary levels of adrenalin and noradrenalin often measure as 24-h excretions *(89,90)*. Fractionated plasma metanephrines show the highest sensitivity, 97%, and can be test of choice in high risk children. VMA (vanillylmandelic acid) and HVA (homovanillic acid) have a too low sensitivity to rule out pheochromocytoma *(91)*. Imaging includes ultrasound, CT, or abdominal MRI depending on local facilities. All these methods can in most cases define the tumor, but MRI seems to be the method of choice *(92)*. Whole-body metaiodobenzylguanidine (MIBG) ^{123}I scan has an important role in helping with the diagnosis and to evaluate the extent of the disease, including defining multiple occurrences and relapsing lesions. Its sensitivity seems, however, not to be better than 80–90% but the specificity approaches 100% *(93,94)*. Labeled somatostatin is an alternative method that has been used in cases with negative MIBG. A biopsy before

surgery should normally be avoided as handling of the tumor can lead to release of catecholamines with severe peaks of high blood pressure leading to stroke or arrhythmias.

The blood pressure is best controlled by the combination of an α- and β-sympathetic blockade often using phenoxybenzamine and a short-acting β-blocking agent as propranolol *(82,95)*. The α-adrenoceptor blockade opposes the vasoconstriction that is induced by the catecholamine excess while the β-blockade opposes reflex tachycardia that can occur from the vasodilatation. β-Blockade on its own should not be used as it can result in worsening blood pressure from not blocking the α-receptors.

Induction of anesthesia and manipulation of the tumor can cause unpredictable release of catecholamines that can cause hypertensive crisis with stroke and arrhythmias. It is important that the above-mentioned pharmacological blockade is in place before the surgery. Liberal salt intake and keeping the child well hydrated is important to reduce surgical risks *(96)*. Metyrosine that competitively inhibits catecholamine biosynthesis can also have a role in minimizing intra-operative risks *(97)*. A very gentle anesthetic procedure keeping the patient very calm is also very important. Acute rises of the blood pressure during surgery might need to be controlled with intravenous antihypertensives. Hypotension can also occur when the venous drainage of the tumor is blocked and the tumor is removed. Treatment with pressor agents such as dopamine or catecholamines might be needed in that situation. Postoperative hypoglycemia should be monitored for *(96)*. Recently, laparoscopic surgery of abdominal and thoracic tumors has become more common *(88,96,98,99)*.

The histopathology of the tumor is important to confirm the diagnosis but cannot accurately predict the further behavior of the tumors. There are attempts to try to quantify the risk of malignancy with a combination of pathological criteria and expression of certain markers that can be helpful in understanding the long-term prognosis *(84)*. Long-term follow-up is needed throughout life to detect tumor relapses and development of tumors at other sites. Screening is done by regular blood pressure measurements and regular monitoring of urinary or plasma catecholamines. This is particularly important in children with defined genetic mutations *(85)*.

Corticosteroid Excess

The most common cause for hypertension from corticosteroid excess is treatment with glucocorticoids. In these children the high blood pressure can be a problem necessitating treatment with multiple antihypertensive medications. The pathophysiology is uncertain but activation of the renin–angiotensin system and sodium retention due to mineralocorticoid effects of the steroid are most often thought to be involved. This form of hypertension will resolve when it is possible to reduce doses or discontinue the medication completely.

Cushing's syndrome caused by excessive production of ACTH or glucocorticoids is far less common in children *(100,101)*. This can be caused by an ACTH-secreting hypothalamic tumor, by ACTH production elsewhere, or by corticosteroid-producing tumors or adrenal hyperplasia. The diagnosis can in these unusual cases mostly be suspected from the classical clinical habitus; round face, truncal obesity, acne, and abdominal striae. These children do also display delayed growth and sometimes virilization and pseudoprecocious puberty *(102)*. In infants McCune–Albright syndrome is a major cause of Cushing's syndrome *(103)*.

The diagnosis is confirmed by urine and blood testing of cortisol and ACTH levels *(104)*. Surgical resection is usually curative but can be very challenging. The hypothalamic lesions should be treated with a transsphenoidal approach *(105)*.

Raised levels of aldosterone from adrenal tumors (Conn's syndrome) are extremely rare conditions in children *(106)*. The mineralocorticoid excess leads to salt and water retention. The condition should be suspected in cases with low to low normal serum potassium and metabolic alkalosis. Surgical treatment should be curative.

Congenital adrenal hyperplasia, in particular the 11β-hydroxylase deficiency and the much less common 17α-hydroxylase deficiency, can cause hypertension *(107,108)* (see also Chapter 6). The 11β-hydroxylase defect leads to decreased secretion of cortisone and cortisol and excess production androgens. This stimulates secretion of pituitary ACTH and excess adrenal production of DOC (11-deoxycorticosterone) that has mineralocorticoid effects in high concentrations. These children also exhibit symptoms of virilization and ambiguous genitalia.

Children with 17α-hydroxylase deficiency lack both cortisol and androgens and are thus not virilized and often not diagnosed before they develop their hypertension, hypokalemia, and hypogonadism in adolescence *(109)*.

Other very uncommon causes of real or apparent mineralocorticoid excess (AME) are Liddle's syndrome, glucocorticoid-remediable aldosteronism (GRA), and Gordon's syndrome. These syndromes that have taught us a lot on molecular mechanisms and tubular function are described in more detail in Chapter 6.

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21 Neonatal Hypertension

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Contents

INTRODUCTION

Hypertension as a clinical problem in newborn infants was first recognized in the 1970s *(1)*. However, recent advances in our ability to identify, evaluate, and care for premature infants have lead to an increased awareness of neonatal hypertension, not only in the neonatal intensive care unit (NICU) but also in the neonatal follow-up clinic. This chapter will focus on the differential diagnosis of hypertension in the neonate, the optimal diagnostic evaluation, and both acute and chronic antihypertensive therapy.

INCIDENCE/EPIDEMIOLOGY

It is difficult to ascertain the actual incidence of hypertension in neonates because there is no generally accepted definition of hypertension for this age group *(2,3)*. One study of preterm infants admitted to six NICUs in New England demonstrated that 28% of infants with birth weights <1500 g had at least one blood pressure that was considered "hypertensive" *(2)*. Clearly, few of these infants had sustained hypertension. At the other extreme, hypertension is considered so unusual in otherwise healthy term infants that routine blood pressure determination is not recommended for this group by consensus organizations *(4)*.

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_21
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Despite these issues, most authors agree that the actual incidence of hypertension in neonates is quite low, ranging from 0.2 to 3% in most reports *(5–9)*. The incidence may be somewhat higher in premature and otherwise high-risk newborns. In a review of over 3000 infants admitted to a Chicago NICU, the overall incidence of hypertension was found to be 0.81% *(8)*. Hypertension was considerably more common in infants with bronchopulmonary dysplasia, patent ductus arteriosus, intraventricular hemorrhage or that had indwelling umbilical arterial catheters. In this latter group, approximately 9% of the infants with these conditions developed hypertension. Similar risk factors for hypertension were identified in a recent study of approximately 2600 infants admitted to a tertiary NICU in Canberra, Australia *(9)*. Aside from prematurity, umbilical artery catheterization, chronic lung disease, and antenatal steroid administration were the most significant risk factors for the development of hypertension *(9)*.

These high-risk infants are also at risk for the development of hypertension long after discharge from the NICU. In a retrospective review of over 650 infants seen in follow-up after discharge from a teaching hospital NICU, Friedman and Hustead found an incidence of hypertension (defined as a systolic blood pressure >113 mmHg on three consecutive visits over 6 weeks) of 2.6% *(10)*. Hypertension in this study was detected at a mean age of approximately 2 months post-term when corrected for prematurity. The hypertensive infants tended to have lower initial Apgar scores and slightly longer NICU stays than infants who remained normotensive, indicating a somewhat greater likelihood of developing hypertension in sicker babies, a finding similar to that of Singh et al. *(8)*.

In yet another study of NICU "graduates," risk factors for higher blood pressure were found to include difficult delivery, prolonged ventilatory support, and hypertension in the nursery *(11)*. Nephrocalcinosis has also been described as a risk factor for future hypertension in infancy *(12)*. Even with the increasing rates of survival of premature infants, however, hypertension remains a relatively infrequent clinical problem that is primarily confined to the NICU or neonatal follow-up clinic.

DIFFERENTIAL DIAGNOSIS

As in older infants and children, the causes of hypertension in neonates are numerous (Table 1), with the two largest categories being renovascular and other renal parenchymal diseases. More specifically, umbilical artery catheter-associated thromboembolism affecting either the aorta or the renal arteries probably accounts for the majority of cases of hypertension seen in the typical NICU. A clear association between use of umbilical arterial catheters and development of arterial thrombi was first demonstrated in the early 1970s by Neal and colleagues *(13)*. They performed aortography at the time of umbilical artery removal in 19 infants, demonstrating thrombus formation in 18 of the 19 infants, as well as several instances of clot fragmentation and embolization. Thrombosis was also seen at autopsy in 7 of 12 additional infants who had died, for an overall incidence of 25 out of 31 infants, or approximately 81% of infants studied.

Following Neal's report, the association between umbilical arterial catheter-associated thrombi and the development of neonatal hypertension was confirmed by several other investigators *(14–19)*. Hypertension was demonstrated in infants who had undergone umbilical arterial catheterization even when thrombi were unable to be demonstrated in the renal arteries. Reported rates of thrombus formation have generally been much lower than in Neal's study, typically about 25% *(14,20,21)*. Although there have been several studies that have examined the duration of line placement and line position ("low" vs. "high") as

Table 1
Causes of Neonatal Hypertension

- Renovascular
  - Thromboembolism
  - Renal artery stenosis
  - Mid-aortic coarctation
  - Renal venous thrombosis
  - Compression of renal artery
  - Abdominal aortic aneurysm
  - Idiopathic arterial calcification
  - Congenital rubella syndrome
- Renal parenchymal disease
  - Congenital
    - Polycystic kidney disease
    - Multicystic-dysplastic kidney disease
    - Tuberous sclerosis
    - Ureteropelvic junction obstruction
    - Unilateral renal hypoplasia
    - Primary megaureter
    - Congenital nephrotic syndrome
    - Renal tubular dysgenesis
  - Acquired
    - Acute tubular necrosis
    - Cortical necrosis
    - Interstitial nephritis
    - Hemolytic-uremic syndrome
    - Obstruction (stones, tumors)
- Pulmonary
  - Bronchopulmonary dysplasia
  - Pneumothorax
- Cardiac
  - Thoracic aortic coarctation
- Endocrine
  - Congenital adrenal hyperplasia
  - Hyperaldosteronism
  - Hyperthyroidism
  - Pseudohypoaldosteronism type II (Gordon syndrome)
- Medications/intoxications
  - Infant
    - Adrenergic agents
    - Caffeine
    - Dexamethasone
    - Erythropoietin
    - Pancuronium
    - Phenylephrine
    - Theophylline
    - Vitamin D intoxication
  - Maternal
    - Cocaine
    - Heroin
- Neoplasia
  - Wilms tumor
  - Mesoblastic nephroma
  - Neuroblastoma
  - Pheochromocytoma
- Neurologic
  - Pain
  - Intracranial hypertension
  - Seizures
  - Familial dysautonomia
  - Subdural hematoma
- Miscellaneous
  - Total parenteral nutrition (TPN)
  - Closure of abdominal wall defect
  - Adrenal hemorrhage
  - Hypercalcemia
  - Traction
  - ECMO
  - Birth asphyxia

factors involved in thrombus formation, these data have not been conclusive *(20,21)*. Thus, the assumption has been made that the cause of hypertension in such cases is related to thrombus formation at the time of line placement, probably related to disruption of the vascular endothelium of the umbilical artery. Such thrombi may then embolize to the kidneys, causing areas of infarction and increased renin release. A similar phenomenon has been reported in infants with dilatation of the ductus arteriosus *(22)*.

The Cochrane Group has regularly examined the controversy regarding umbilical artery catheter placement and complications *(23)*. They analyzed five randomized clinical trials and one study using alternate assignments to compare the incidence of complications such as thrombus formation. The placement of a catheter tip was defined as high when located in the descending aorta above the diaphragm and low when located in the descending aorta above the bifurcation but below the renal arteries. The reviewers concluded that high catheter position causes fewer clinically obvious ischemic complications and possibly decreases the frequency of aortic thrombosis. As far as hypertension was concerned, however, it was concluded that it seems to appear with equal frequency among infants with high and low umbilical artery catheter placements.

Other renovascular problems may also lead to neonatal hypertension. Renal venous thrombosis (Fig. 1) classically presents with the triad of hypertension, gross hematuria, and an abdominal mass. Hypertension may be quite severe in such cases and may persist beyond the neonatal period *(24–26)*. Fibromuscular dysplasia leading to renal arterial stenosis is another important cause of renovascular hypertension in the neonate. Many of these infants may have main renal arteries that appear normal on angiography but demonstrate significant branch vessel disease that can cause severe hypertension *(27–29)*. In addition, renal arterial stenosis may also be accompanied by mid-aortic coarctation and cerebral vascular stenoses *(27,30)*. Other vascular abnormalities may also lead to hypertension in the neonate, including idiopathic arterial calcification *(31,32)* and renal artery stenosis secondary to congenital rubella infection *(33)*. Congenital aortic aneurysm is a rare condition producing renovascular hypertension that may be fatal because of intractable congestive heart failure *(34)*. Finally, mechanical compression of one or both renal arteries by tumors, obstructed/hydronephrotic kidneys, or other abdominal masses may also lead to hypertension.

The next largest group of infants with hypertension are those who have congenital renal parenchymal abnormalities. It is well known that both autosomal dominant and autosomal recessive polycystic kidney disease (PKD) may present in the newborn period with severe nephromegaly and hypertension *(35–37)*. With recessive PKD (Fig. 2), the majority of affected infants will be discovered to be hypertensive during the first year of life, and presentation in the first month of life is common *(35,36)*. The most severely affected infants with recessive PKD are at risk for development of congestive heart failure due to severe, malignant hypertension. Although much less common than in PKD, hypertension has also

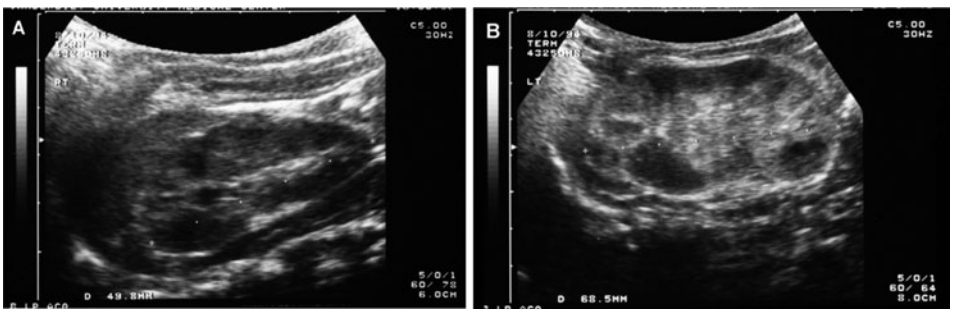

Fig. 1. Renal venous thrombosis. (**a**) Renal ultrasound demonstrating normal right kidney. (**b**) Renal ultrasound demonstrating affected left kidney. The kidney is enlarged and swollen, with loss of normal corticomedullary differentiation.

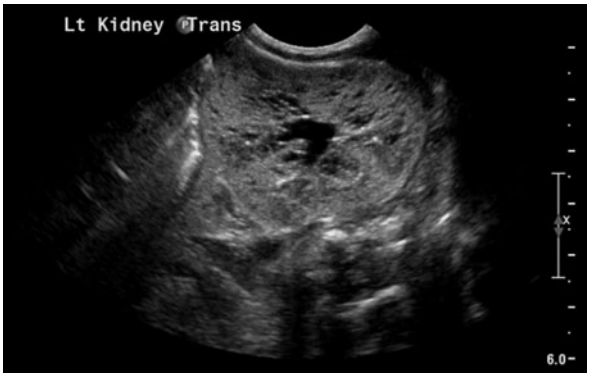

Fig. 2. Transverse ultrasound image demonstrating increased echogenicity, loss of corticomedullary differentiation, and medullary microcyst formation classic of autosomal recessive polycystic kidney disease.

been reported in infants with unilateral multicystic-dysplastic kidneys *(6,38–40)*. This is somewhat paradoxical, as such kidneys are usually thought to be non-functioning. In fact, the case has been made that hypertension in such patients is the result of another coexisting urologic abnormality such as parenchymal scarring *(41)*. Another recently described cause of severe neonatal hypertension related to dysplasia is unilateral tubular dysgenesis *(42)*.

Renal obstruction may be accompanied by hypertension, even in the absence of renal arterial compression. This has been seen, for example, in infants with congenital ureteropelvic junction obstruction *(6,8,9,43)* and sometimes may persist following surgical correction of the obstruction *(44)*. Hypertension has also been described in babies with congenital primary megaureter *(45)*. Ureteral obstruction by other intra-abdominal masses may also be accompanied by hypertension. The mechanism of hypertension in such instances is unclear, although the renin–angiotensin system has been implicated *(46,47)*. Finally, unilateral renal hypoplasia may also present with hypertension *(48)*, although this is uncommon. The importance of congenital urologic malformations as a cause of neonatal hypertension was recently highlighted in a referral series from Brazil *(43)*. In that series, 13/15 infants with hypertension had urologic causes. Median age at diagnosis of hypertension was 20 days (range 5–70 days), emphasizing the need for regular BP measurement in infants with urologic malformations in order to detect hypertension *(49)*.

Hypertension due to acquired renal parenchymal disease is less common than that due to congenital renal abnormalities. However, severe ATN, interstitial nephritis, or cortical necrosis may be accompanied by significant hypertension *(6,8)* usually on the basis of volume overload or presumed activation of the renin–angiotensin system. Hemolytic uremic syndrome, which has been described in both term and preterm infants *(50)*, is usually also accompanied by hypertension. Such hypertension may be extremely difficult to control, requiring treatment with multiple agents.

Hypertension as a consequence of bronchopulmonary dysplasia (BPD) was first described in the mid-1980s by Abman and colleagues *(51)*. In a study of 65 infants discharged from a neonatal intensive care unit, the instance of hypertension in infants with BPD was 43% vs. an incidence of 4.5% in infants without BPD. Investigators were unable to identify a clear cause of hypertension, but postulated that hypoxemia might be involved. Over half of the infants with BPD who developed hypertension did not display it until

after discharge from the NICU, highlighting the need for measurement of blood pressure in NICU "graduates," whether or not they have lung disease *(9,49)*.

Abman's findings have been reproduced by other investigators, most recently in 1998 by Alagappan *(52)*, who found that hypertension was twice as common in very low birth weight infants with BPD compared to the incidence in all very low birth weight infants. Since all of the hypertensive infants required supplemental oxygen and aminophylline, development of hypertension appeared to be correlated with the severity of pulmonary disease. Anderson and colleagues have demonstrated that the more severe the bronchopulmonary dysplasia, the higher the likelihood of the development of increased blood pressure *(53)*. Severity was defined as a greater need for diuretics (91% of the hypertensive group vs. 55% of the normotensive group, $p<0.05$) and bronchodilators (91% of the hypertensive group vs. 37% of the normotensive group, $p<0.001$).

Although updated studies are needed, these observations reinforce the impression that infants with severe BPD are clearly at increased risk and need close monitoring for the development of hypertension. This is especially true in infants who require ongoing treatment with theophylline preparations and/or corticosteroids.

Hypertension may also be seen in disorders of several other organ systems. Coarctation of the thoracic aorta is easily detected in the newborn period and has been reported in numerous case series of neonatal hypertension. Hypertension may persist in these infants even after surgical repair of the coarctation. Repair early in infancy seems to lead to an improved long-term outcome compared to delayed repair *(54)*. Endocrine disorders, particularly congenital adrenal hyperplasia, hyperaldosteronism, and hyperthyroidism, constitute easily recognizable clinical entities that have been reported to cause hypertension in neonates *(55–58)*. Similarly, pseudohypoaldosteronism type II (Gordon syndrome) should be suspected in the hypertensive infant with hyperkalemia and metabolic acidosis. The interested reader should consult Chapter 6 for a full discussion of Gordon syndrome and other monogenic forms of hypertension, some of which may present in infancy.

Iatrogenic causes of hypertension comprise another important category of diagnoses. Medications commonly administered to infants for the treatment of pulmonary disease such as dexamethasone and aminophylline have clearly been shown to elevate blood pressure *(59–61)*. The risks of dexamethasone-induced hypertension have been clearly illustrated in a multicenter study conducted by the Neonatal Research Network *(61)*. In this study of 220 very low birth weight infants (birth weight 501–1000 g) randomized to receive either dexamethasone or placebo because of the need for mechanical ventilation, the incidence of systolic BP >90 mmHg was significantly higher in the dexamethasone group ($p=0.01$ compared to placebo), as was the likelihood of being treated for hypertension ($p=0.04$).

In addition, high doses of adrenergic agents, prolonged use of pancuronium, or administration of phenylephrine ophthalmic drops *(62)* may raise blood pressure. Erythropoietin therapy has also been implicated in the development of neonatal hypertension *(63)*. Hypertension in these infants typically resolves when the offending agent is discontinued or its dose reduced. For infants receiving prolonged parenteral nutrition (TPN), hypertension may result from salt and water overload, or from hypercalcemia, caused either directly by excessive calcium intake or indirectly by vitamin A or D intoxication.

Substances ingested during pregnancy may also lead to significant problems with hypertension in the neonate. In particular, maternal cocaine use may have a number of undesirable effects on the developing kidney that may lead to hypertension *(64)*. Hypertension has also been reported to occur in infants of drug-addicted mothers withdrawing from heroin.

Tumors, including neuroblastoma, Wilms tumor, and mesoblastic nephroma, may all present in the neonatal period and may produce hypertension, either because of compression of the renal vessels or ureters or because of production of vasoactive substances such as renin or catecholamines *(9,65–69)*. Neurologic problems such as seizures, intracranial hypertension, and pain constitute fairly common causes of episodic hypertension. In the typical modern NICU, postoperative pain must not be overlooked as a cause of hypertension. Provision of adequate analgesia may constitute the only required "antihypertensive medication" in such infants.

There are numerous other miscellaneous causes of hypertension in neonates (Table 1). Of these, hypertension associated with extracorporeal membrane oxygenation (ECMO) deserves comment. This may be seen in up to 50–90% of infants requiring ECMO *(70–72)* and may result in serious complications, including intracranial hemorrhage *(73)* and increased mortality *(71)*. Multiple antihypertensive medications may be needed to achieve blood pressure control *(72)*. Despite extensive investigation, the exact pathogenesis of this form of hypertension remains poorly understood. Fluid overload, altered handling of sodium and water, activation of the renin–angiotensin system, and derangements in atrial baroreceptor function have all been proposed as causative factors *(72)*. Given the widespread and increasing use of ECMO both in neonates and in older children, further investigation of this problem is clearly needed.

DEFINITION OF HYPERTENSION

Establishing a definition for hypertension in neonates is difficult due to the rapid changes in blood pressure in the immediate postnatal period and is even more difficult in preterm neonates due to similar issues. Just as blood pressure in older children has been demonstrated to increase with increasing age and body size, studies in both term and preterm infants have demonstrated that blood pressure in neonates increases with both gestational and postconceptual age, as well as with birth weight *(73–79)*. Additionally, blood pressure increases over the first few days of life *(80,81)*, gradually stabilizing by about 5 days of age. Updated normative data for blood pressure in term infants over the first few days of life have recently been published *(81)*.

Extremely useful data describing the various influences on neonatal blood pressure have been published by Zubrow and associates *(78)*, who prospectively obtained serial blood pressure measurements from 695 infants admitted to several NICUs in a large metropolitan area over a period of 3 months. They then defined the mean blood pressures and upper and lower 95% confidence limits for the infants studied. Their data clearly demonstrated that blood pressure increases with increasing gestational age, birthweight, and postconceptual age (Figs. 3, 4, and 5). Since the diagnosis of hypertension in older children is based upon identifying those with blood pressures at the upper end of the distribution (i.e., above the 95th percentile), an approach to identifying hypertension in neonates would be to consider an infant's blood pressure to be elevated if it consistently was above the upper 95% confidence interval for infants of similar gestational or postconceptual age.

For older infants (1–12 months of age) found to be hypertensive following discharge from the NICU or for ongoing follow-up of persistently hypertensive neonates, the percentile curves published in the Second Task Force report (Fig. 6) *(82)* remain the only available reference data. Based on serial blood pressure measurements obtained from nearly 13,000 infants, these curves allow blood pressure to be characterized as normal or elevated not only by age and gender but also by size, albeit to a somewhat limited extent.

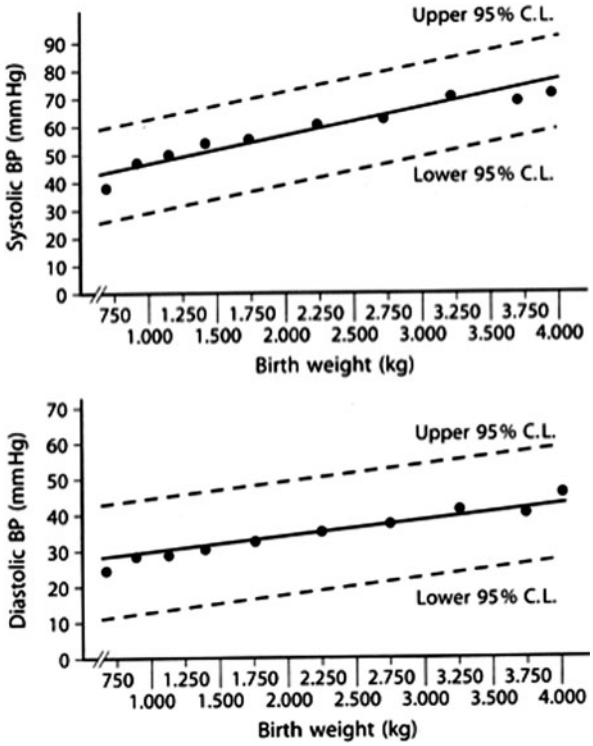

Fig. 3. Linear regression of mean systolic (**a**) and diastolic (**b**) blood pressures by birth weight on day 1 of life, with 95% confidence limits (*upper* and *lower dashed lines*). Reprinted with permission from Macmillan Publishers *(78)*, copyright 1995.

Hypertension in this age group would be defined as blood pressure elevation above the 95th percentile for infants of similar age, size, and gender. Updated normative blood pressure data for this age group are urgently needed and may perhaps be generated by the National Children's Study currently underway in the United States.

BLOOD PRESSURE MEASUREMENT

As in older children, it is crucial that blood pressure is being measured accurately so that hypertensive infants will be correctly identified. Fortunately, in most acutely ill neonates, blood pressure is usually monitored directly via an indwelling arterial catheter either in the radial or in the umbilical artery. This method provides the most accurate BP readings and is clearly preferable to other methods *(83)*. In addition to accurately measuring blood pressures, such catheters are also crucial in careful management of hypertension, particularly in infants with extremely severe blood pressure elevation. This will be discussed in more detail later in the chapter.

Automated, oscillometric devices are the most common alternative method of blood pressure measurement in most NICUs. Although accurate, readings obtained by such devices may differ significantly from intra-arterial readings. When comparing blood pressures obtained from 31 newborns with these two techniques, Low et al. *(84)* reported that the average oscillometric pressures were significantly lower than the intra-arterial

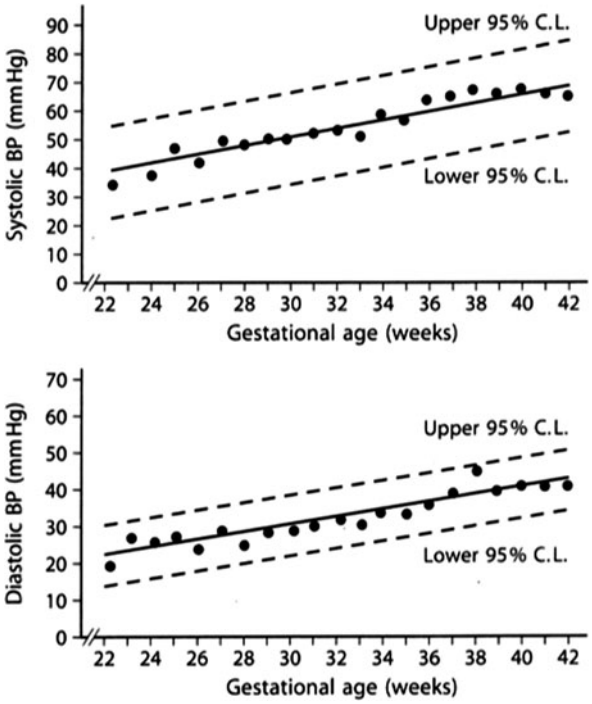

Fig. 4. Linear regression of mean systolic (**a**) and diastolic (**b**) blood pressures by gestational age on day 1 of life, with 95% confidence limits (*upper* and *lower dashed lines*). Reprinted with permission from Macmillan Publishers *(78)*, copyright 1995.

pressures. The systolic was lower by 1 mmHg, the mean by 5.3 mmHg, and the diastolic by 4.6 mmHg. These differences may need to be taken into account when determining whether an infant's blood pressure is normal or elevated.

Despite the fact that blood pressure readings obtained by oscillometric devices may differ slightly from intra-arterial BP measurements, they are easy to use and provide the ability to follow blood pressure trends over time. They are especially useful for infants who require BP monitoring after discharge from the NICU *(85)*. When using such devices, however, attention should be paid to using a properly sized cuff and also to the extremity used. Most normative blood pressure data, not only in infants but also in older children, have been collected using blood pressures obtained in the right arm *(82)*. Since blood pressures obtained in the leg may be higher than those obtained in the arm *(6–87)*, the use of other extremities for routine blood pressure determination may complicate the evaluation of hypertension. Nursing staff should document the extremity used for blood pressure determinations and try to use the same extremity for subsequent determinations if possible. Finally, the infant's state of activity may also affect the accuracy of BP readings. Increased activity, including oral feeding, increases blood pressure *(88)*. It may therefore be important to obtain BP readings while infants are sleeping in order to obtain the most accurate readings.

These issues have been highlighted in a study by Nwanko et al. of blood pressure in low birth weight term and preterm infants *(89)*. It was demonstrated that blood pressure was significantly lower in the prone than supine position and that the first reading was significantly higher than the third. Nwanko et al. concluded that a standardized protocol

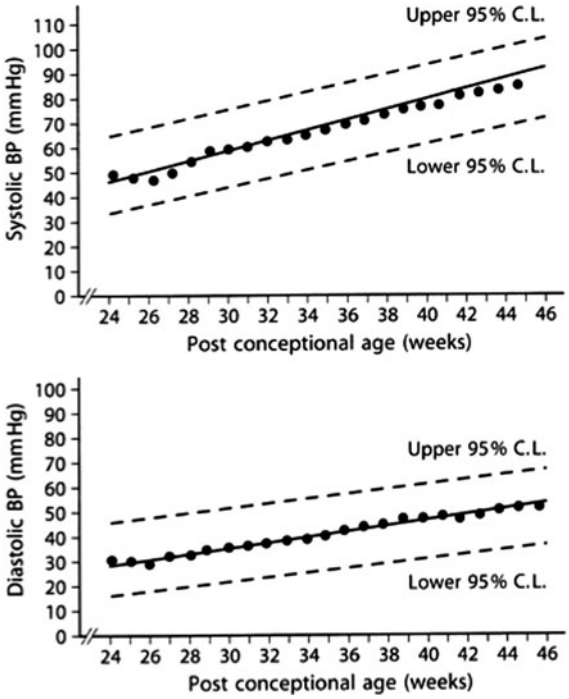

Fig. 5. Linear regression of mean systolic (**a**) and diastolic (**b**) blood pressures by postconceptual age in weeks, with 95% confidence limits (*upper* and *lower dashed lines*). Reprinted with permission from Macmillan Publishers *(78)*, copyright 1995.

is necessary in order to accurately measure BP in neonates. They recommended checking blood pressures 1.5 h after the last feeding or intervention, applying an appropriately sized cuff (two-thirds the length of the limb segment and 75% of the limb circumference), waiting 15 more minutes for stillness, then obtaining three successive readings at 2-min intervals. Using proper technique, it should be possible to correctly identify infants with hypertension requiring further evaluation.

DIAGNOSTIC EVALUATION

Diagnosing the etiology of hypertension is a straightforward task in most hypertensive neonates. A relatively focused history should be obtained, paying attention to determining whether there were any pertinent prenatal exposures, as well as to the particulars of the infant's nursery course and any concurrent conditions. The procedures that the infant has undergone (e.g., umbilical catheter placement) should be reviewed, and the current medication list should be scrutinized.

The physical examination, likewise, should be focused on obtaining pertinent information to assist in narrowing the differential diagnosis. Blood pressure readings should be obtained in all four extremities in order to rule out coarctation of the thoracic aorta. The general appearance of the infant should be assessed, with particular attention paid to the presence of dysmorphic features that may indicate an obvious diagnosis such as congenital adrenal hyperplasia. Careful cardiac and abdominal examination should be performed. The

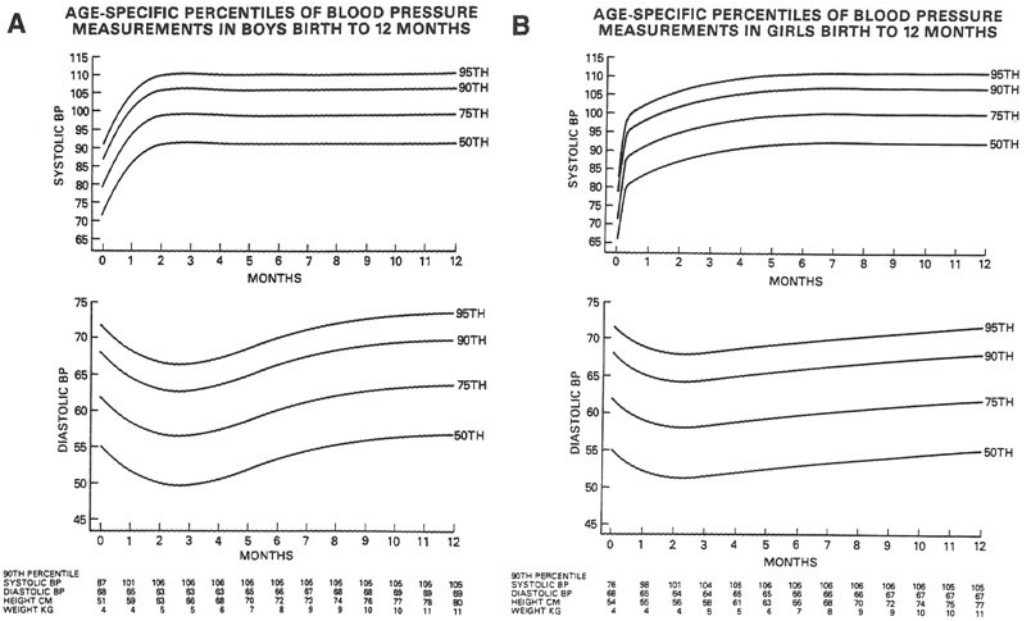

Fig. 6. Age-specific percentiles for blood pressure in boys (**a**) and girls (**b**) from birth to 12 months of age. Reprinted from Task Force on Blood Pressure Control in Children *(82)*, National Heart, Lung and Blood Institutes, National Institutes of Health, Bethesda, MD.

presence of a flank mass or of an epigastric bruit may point the clinician toward diagnosis of either ureteropelvic junction obstruction or renal artery stenosis, respectively.

In most instances, few laboratory data are needed in the evaluation of neonatal hypertension, as the correct diagnosis is usually suggested by the history and physical examination. It is important to assess renal function, as well as to examine a specimen of the urine in order to ascertain the presence of renal parenchymal disease. Chest X-ray may be useful as an adjunctive test in infants with congestive heart failure or in those with a murmur on physical examination. Other diagnostic studies, such as cortisol, aldosterone, or thyroxine levels, should be obtained when there is history suggesting endocrine hypertension (Table 2).

Determination of plasma renin activity is frequently recommended in the assessment of neonates with hypertension, although there are few data on what constitutes normal values for infants, particularly for premature infants. Available data indicate that renin values are typically quite high in infancy, at least in term newborns *(90,91)*. Although renal artery stenosis and thromboembolic phenomenon are typically considered high-renin forms of hypertension, a peripheral renin level may not be elevated in such infants despite the presence of significant underlying pathology. Conversely, plasma renin may be falsely elevated by medications that are commonly used in the NICU, such as aminophylline *(92)*. At the other end of the spectrum, plasma renin activity will be profoundly suppressed in some genetic forms of hypertension (see Chapter 6). With proper interpretation, assessment of plasma renin activity may be helpful in the evaluation of some infants and is therefore usually included as part of the initial laboratory evaluation.

The role of various imaging modalities in the evaluation of neonatal hypertension has been reviewed in detail elsewhere *(93)*, so only a few comments will be made here.

Table 2
Diagnostic Testing in Neonatal Hypertension

Generally useful	*Useful in selected infants*
Urinalysis (and/or culture)	Thyroid studies
CBC and platelet count	Urine VMA/HVA
Electrolytes	Aldosterone
BUN, creatinine	Cortisol
Calcium	Echocardiogram
Plasma renin	Abdominal/pelvic ultrasound
Chest X-ray	VCUG
Renal ultrasound with Doppler	Aortography and/or renal arteriography
	Nuclear scan (DTPA/Mag-3)

Ultrasound imaging of the genitourinary tract is a relatively inexpensive, noninvasive, and quick study that should be obtained in all hypertensive infants. An accurate renal ultrasound can help uncover potentially correctable causes of hypertension such as renal venous thrombosis *(24)*, may detect aortic and/or renal arterial thrombi *(14)*, and can identify anatomic renal abnormalities or other congenital renal diseases. Doppler evaluation should be added, especially in acutely hypertensive infants, primarily to identify absent venous flow, which is diagnostic of renal venous thrombosis. For these reasons, ultrasound has largely replaced intravenous pyelography, which has little if any use in the routine assessment of neonatal hypertension.

For infants with extremely severe blood pressure elevation, angiography may be necessary. A formal angiogram utilizing the traditional femoral venous approach offers the most accurate method of diagnosing renal arterial stenosis, particularly given the high incidence of intrarenal branch vessel disease in children with fibromuscular dysplasia *(27,28)*. Even though there have been significant advances in both computed tomographic and magnetic resonance angiography, these techniques still cannot provide detailed images of branch vessels in infants and young children *(28,29)*. In extremely small infants, or where appropriate facilities are not available, it may be necessary to defer angiography, managing the hypertension medically until the baby is large enough for an angiogram to be performed safely.

Although nuclear scanning has been shown in some studies to demonstrate abnormalities of renal perfusion caused by thromboembolic phenomenon, in our practice it has had little role in the assessment of infants with hypertension, primarily due to the difficulties in obtaining accurate, interpretable results in this age group. In proper hands, it may be useful as an adjunctive study in the evaluation of infants with suspected renovascular hypertension *(93)*. Other imaging studies, including echocardiograms and voiding cystourethrograms, should be obtained as clinically indicated.

TREATMENT

With a few exceptions (for example, congestive heart failure) generally accepted indications for treatment of hypertensive neonates have not been established. It is there-

fore up to the individual clinician to decide which infants should receive antihypertensive medications. Although long-term follow-up data of untreated hypertensive infants are not available, it is reasonable to assume that as in older children, long-standing hypertension in the neonate may cause left ventricular hypertrophy or other target organ damage. Therefore, consideration should be given to treatment of any infant with sustained hypertension (as defined above).

Although today's clinician has available an ever-expanding list of agents that can be used for treatment of neonatal hypertension (Table 3), practically none of these medications have been systematically studied in neonates, and there are no antihypertensive medications with FDA-approved indications for use in hypertensive infants. It is unfortunate that infants remain excluded from the clinical trials of antihypertensive agents that have been conducted in children under the auspices of the 1997 Food and Drug Administration Modernization Act *(94)*. Physicians who care for hypertensive neonates must therefore rely upon case series data, older clinical trials, and personal experience for guidance in selecting the appropriate agent for a particular neonate.

Prior to initiating antihypertensive drug therapy, however, the infant's clinical status should be assessed and any easily correctable iatrogenic causes of hypertension addressed. These may include infusions of inotropic agents or administration of other medications known to elevate blood pressure, volume overload, or pain. Following this, an antihypertensive agent should be chosen that is not only appropriate for the specific clinical situation but also directed to the pathophysiology of the infant's hypertension whenever possible.

For the majority of acutely ill infants, particularly those with severe hypertension, continuous intravenous infusions are the most appropriate approach. The advantage of intravenous infusions are numerous, most importantly including the ability to quickly increase or decrease the rate of infusion to achieve the desired level of blood pressure control. Infusions may also allow the infant's blood pressure to be kept within a relatively narrow range. This stands in stark contrast to the wide fluctuations in blood pressure frequently seen when intermittently administered intravenous agents are utilized. As in patients of any age with malignant hypertension, care should be taken to avoid too rapid a reduction in blood pressure *(95)* in order to avoid cerebral ischemia and hemorrhage, a problem that premature infants in particular are already at increased risk for due to the immaturity of their periventricular circulation. Here again, continuous infusions of intravenous antihypertensives offer a distinct advantage over intermittently administered agents.

Although comprised of single-center, retrospective studies, a growing body of literature suggests that the intravenous calcium channel antagonist nicardipine is appropriate for use as a first-line agent in severely hypertensive infants *(96–98)*. This drug offers the advantage of quick onset of action, which allows the patient's blood pressure to be easily titrated to and maintained at the desired level *(99)*. It may also be continued for prolonged periods of time without apparent decrease in antihypertensive efficacy *(98)*. Other intravenous antihypertensives that have been successfully used in neonates include esmolol *(100)*, labetalol, and nitroprusside *(101)*. Whatever agent is used, blood pressure should be monitored continuously via an indwelling arterial catheter or else by frequently repeated (Q10–15 min) cuff readings so that the dose can be titrated to achieve the desired degree of blood pressure control.

For some infants, intermittently administered intravenous agents do have a role in therapy. Hydralazine and labetalol in particular may be useful in infants with mild-to-moderate hypertension that are not yet candidates for oral therapy because of gastrointestinal dysfunction. Enalaprilat, the intravenous angiotensin-converting enzyme

Table 3
Recommended Doses for Selected Antihypertensive Agents for Treatment of Hypertensive Infants

Class	*Drug*	*Route*	*Dose*	*Interval*	*Comments*
ACE inhibitors	Captopril	Oral	<3months: 0.01–0.5 mg/kg/dose Max 2 mg/kg/day >3months: 0.15–0.3 mg/kg/dose Max 6 mg/kg/day	TID	1. First dose may cause rapid drop in BP, especially if receiving diuretics 2. Monitor serum creatinine and K^+ 3. Intravenous enalaprilat *not* recommended—see text
	Enalapril	Oral	0.08–0.6 mg/kg/day	QD–BID	
	Lisinopril	Oral	0.07–0.6 mg/kg/day	QD	
α- and β-antagonists	Labetalol	Oral	0.5–1.0 mg/kg/dose Max 10 mg/kg/day	BID-TID	Heart failure, BPD relative contraindications
		IV	0.20–1.0 mg/kg/dose 0.25–3.0 mg/kg/h	Q4–6 h Infusion	
	Carvedilol	Oral	0.1 mg/kg/dose up to 0.5 mg/kg/dose	BID	May be useful in heart failure
β-Antagonists	Esmolol	IV	100–500 mcg/kg/min	Infusion	Very short-acting—constant infusion necessary
	Propranolol	Oral	0.5–1.0 mg/kg/dose Max 8–10 mg/kg/day	TID	Monitor heart rate; avoid in BPD
Calcium channel blockers	Amlodipine	Oral	0.05–0.3 mg/kg/dose Max 0.6 mg/kg/day	QD	All may cause mild reflex tachycardia
	Isradipine	Oral	0.05–0.15 mg/kg/dose Max 0.8 mg/kg/day	QID	
	Nicardipine	IV	1–4 mcg/kg/min	Infusion	

Table 3
(continued)

Class	*Drug*	*Route*	*Dose*	*Interval*	*Comments*
Central α-agonist	Clonidine	Oral	5–10 mcg/kg/day Max 25 mcg/kg/day	TID	May cause mild sedation
Diuretics	Chlorothiazide	Oral	5–15 mg/kg/dose	BID	Monitor electrolytes
	Hydrochlorothiazide	Oral	1–3 mg/kg/dose	QD	
	Spironolactone	Oral	0.5–1.5 mg/kg/dose	BID	
Vasodilators	Hydralazine	Oral	0.25–1.0 mg/kg/dose Max 7.5 mg/kg/day	TID–QID	Tachycardia and fluid retention are common side effects
		IV	0.15– 0.6 mg/kg/dose	Q4h	
	Minoxidil	Oral	0.1–0.2 mg/kg/dose	BID–TID	Tachycardia and fluid retention common side effects; prolonged use causes hypertrichosis
	Sodium nitroprusside	IV	0.5–10 mcg/kg/min	Infusion	Thiocyanate toxicity can occur with prolonged (>72 h) use or in renal failure

Abbreviations: BID, twice daily; BPD, bronchopulmonary dysplasia; IV, intravenous; QD, once daily; QID, four times daily; TID, three times daily.

inhibitor, has also been reported to be useful in the treatment of neonatal renovascular hypertension *(102,103)*, despite the lack of an established safe and effective pediatric (let alone neonatal) dose. However, in our experience, this agent should be used with extreme caution, if at all. Even doses at the lower end of published ranges may lead to significant, prolonged hypotension and oliguric acute renal failure in neonates.

Oral antihypertensive agents (Table 3) are best reserved for infants with less severe hypertension or infants whose acute hypertension has been controlled with intravenous infusions and are ready to be transitioned to chronic therapy. Again, no guidelines exist to help choose what agents are appropriate for use in neonates. At least one recent report indicates that ACE inhibitors and calcium channel blockers are common choices in infants requiring oral antihypertensive therapy *(43)*. A recent analysis of a large administrative database of NICU encounters from 36 children's hospitals in the United States indicated that hypertensive neonates are exposed to multiple antihypertensive agents, with direct vasodilators, ACE inhibitors, and calcium channel blockers among the most commonly used classes of agents (D. Blowey MD, Pediatric Academic Societies meeting, Washington, DC, May 14, 2005).

Captopril in particular is a useful agent for many causes of neonatal hypertension *(104,105)* and is commonly used in many NICUs despite the concerns of some pediatric nephrologists about the long-term effects of ACE inhibitors on renal maturation in premature infants. Based on this concern, at our center, captopril is typically avoided until the preterm infant has reached a corrected postconceptual age of 44 weeks. If captopril is chosen, the starting dose should be extremely low, especially in premature infants, as they may have an exaggerated fall in blood pressure following captopril administration. Adverse neurologic effects have been described in infants following captopril-related hypotension *(105)*, highlighting the need for close blood pressure monitoring after administration of this agent. Other ACE inhibitors (enalapril, lisinopril, etc.) have no doubt been used in neonates, but there are no published data on safe and effective doses.

When a vasodilator is indicated, the second-generation calcium channel blocker isradipine may be superior to the older agents hydralazine and minoxidil since it can be compounded into a stable suspension *(106)* that can be dosed with accuracy, even in tiny infants *(107)*. Use of short-acting nifedipine is no longer recommended because of the difficulty in administering small doses and because of the rapid, profound, and short-lived blood pressure reduction typically produced by this agent *(108)*. The third-generation calcium channel blocker amlodipine may also be useful for long-term management of neonatal hypertension. Like isradipine, it may be compounded into a stable suspension and can therefore be dosed accurately, even in small infants *(99)*.

If either an ACE inhibitor such as captopril or a vasodilator is chosen as the initial agent and if the infant's blood pressure is unable to be controlled by that agent alone, the addition of a diuretic will frequently result in the desired degree of blood pressure control. Beta-blockers may need to be avoided in chronic therapy of neonatal hypertension, particularly in infants with chronic lung disease. In such infants, diuretics may have a beneficial effect not only in controlling blood pressure but also in improving pulmonary function *(109)*. Interestingly, we have observed numerous infants with chronic lung disease over the years who "suddenly" became hypertensive after the withdrawal of chronic diuretic therapy. Although this observation is based on anecdotal experience, one could speculate that these infants had chronic lung disease-associated hypertension all along that was being "masked" by the diuretics being prescribed for their lung disease.

Surgery is indicated for treatment of neonatal hypertension in a limited set of circumstances *(110)*. In particular, hypertension caused by ureteral obstruction or aortic coarctation is best approached surgically. For infants with renal arterial stenosis, it may be necessary to manage the infant medically until it has grown sufficiently to undergo definitive repair of the vascular abnormalities *(111)*. However, unilateral nephrectomy may be needed in rare cases *(112)*. Infants with hypertension secondary to Wilms tumor or neuroblastoma will require surgical tumor removal, possibly following chemotherapy. A case has also been made by some authors for removal of multicystic-dysplastic kidneys because of the risk of development of hypertension *(38–40)*, although this is controversial *(41)*. Infants with malignant hypertension secondary to polycystic kidney disease may require bilateral nephrectomy. Fortunately, such severely affected infants are quite rare.

LONG-TERM OUTCOME

Few studies examining the long-term outcome of neonatal hypertension have been published. Fortunately, some data are available for the largest category of hypertensive infants, namely those with hypertension related to an umbilical arterial catheter *(113,114)*. Although better data are needed, available information and personal experience suggest that in such babies, hypertension will usually resolve over time. Some of these infants may require increases in their antihypertensive medications in the first several months following discharge from the nursery as they undergo rapid growth. Following this, it is usually possible to "wean" their antihypertensives by making no further dose increases as the infant continues to grow, followed by later discontinuation of treatment. Home blood pressure monitoring by the parents is a crucially important component of this process. Home blood pressure equipment, usually an oscillometric device, should be arranged for all infants discharged from the NICU on antihypertensive medications, and home blood pressure data should be used in guiding continuation or discontinuation of antihypertensive medications.

Some forms of neonatal hypertension may persist beyond infancy. In particular, PKD and other forms of renal parenchymal disease may continue to cause hypertension throughout childhood *(35–37,115)*. Infants with renal venous thrombosis may also remain hypertensive, and some of these children will ultimately benefit from removal of the affected kidney *(24,25)*. Persistent or late/"recurrent" hypertension may also be seen in children who have undergone repair of renal artery stenosis or thoracic aortic coarctation. Reappearance of hypertension in these situations should prompt a search for restenosis by the appropriate imaging studies.

What are sorely needed at this point are true long-term outcome studies of infants with neonatal hypertension. Since many of these infants are delivered prior to the completion of nephron development, it is possible that they may not develop the full complement of glomeruli normally seen in term infants. Reduced nephron mass has been hypothesized to be a risk factor for the development of hypertension in adulthood *(116,117)*. Thus, it may be possible that hypertensive neonates (and possibly also normotensive premature neonates) are at increased risk compared to term infants for the development of hypertension in late adolescence or early adulthood. Since we are now entering the era in which the first significantly premature NICU "graduates" are reaching their second and third decades of life, it is possible that appropriate studies can be conducted to address this question.

CONCLUSIONS

Blood pressure in neonates depends on a variety of factors, including gestational age, postnatal age, and birth weight. Hypertension can be seen in a variety of situations in the modern NICU and is especially common in infants who have undergone umbilical arterial catheterization or who have chronic lung disease. A careful diagnostic evaluation should lead to determination of the underlying cause of hypertension in most infants. Treatment decisions should be tailored to the severity of the hypertension and may include intravenous and/or oral therapy. Hypertension will resolve in most infants over time, although a small number may have persistent blood pressure elevation throughout childhood. Further study is needed to obtain better normative data on blood pressure in infancy and to define the long-term outcome of hypertensive neonates.

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22 Hypertension in Chronic Kidney Disease

Franz Schaefer, MD

Contents

Kidney disease is the most common identifiable cause of secondary hypertension in childhood. In this chapter, the prevalence, pathophysiology, and treatment of renal hypertension will be reviewed, with an emphasis on recent clinical trial results demonstrating the benefits of aggressive treatment of hypertension on the rate of progression of chronic kidney disease.

PREVALENCE OF RENAL HYPERTENSION IN CHILDHOOD

Numerous recent clinical trials have established that hypertension is one of the earliest and most prevalent complications of pediatric chronic kidney disease (CKD). Among 366 children with CKD followed at a single center, the prevalence of hypertension according to office blood pressure was 70%, increasing from 63% in CKD stage 1 to >80% in stages 3–5 *(1)*. The fraction of patients with uncontrolled hypertension despite antihypertensive treatment increased from 9% in CKD stage 1 to 20% in stage 5. Similarly, in the chronic kidney disease in children (CKiD) study in North America, the prevalence of elevated blood pressure among 432 children with moderate CKD (>90th percentile; based upon auscultatory office BP) was 25% for systolic BP and 23% for DBP *(2)*. A significant proportion of these children were not receiving antihypertensive medications, implying that hypertension in pediatric CKD is frequently missed. Finally, in a cross-sectional multicenter survey of 24-h blood pressure performed by the ESCAPE trial group in 508 children with stages 2–4 CKD,

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_22
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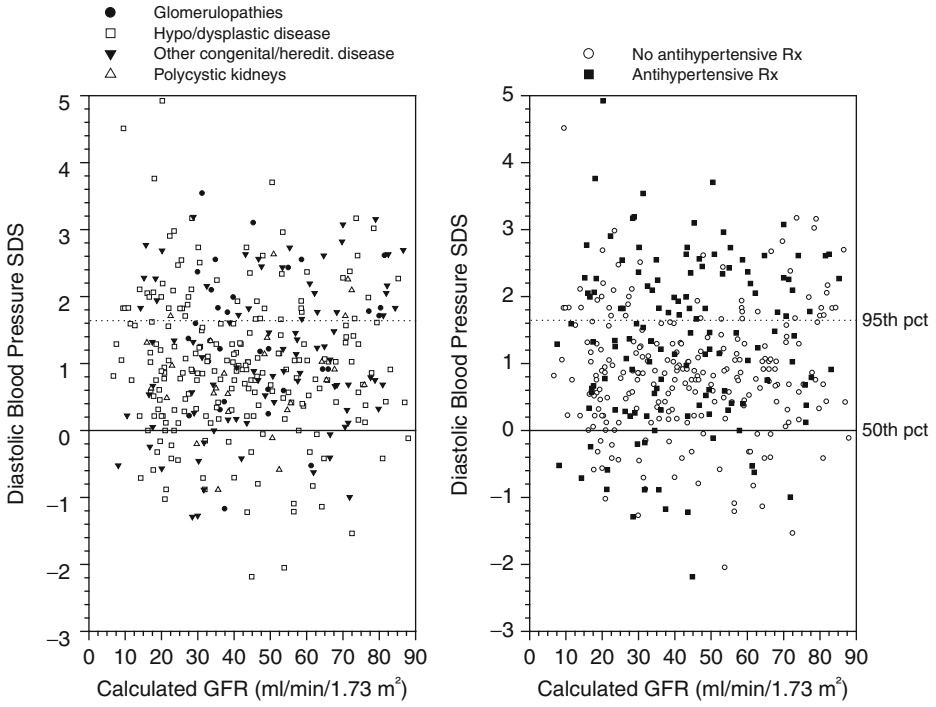

Fig. 1. Blood pressure in 508 children with chronic kidney disease. Distribution of diastolic blood pressure SDS is depicted according to underlying disease (*left panel*) and by prevalent antihypertensive medication (*right panel*). Data were obtained as part of a trial screening procedure in 33 European 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. *(139)*.

the prevalence of controlled or uncontrolled (diastolic) hypertension was 46% (Fig. 1) *(3)*. Among the patients receiving antihypertensive treatment, 30% had elevated blood pressure. Blood pressure was largely independent of the current glomerular filtration rate.

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 *(4,5)*. 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 *(6)*. Fibromuscular dysplasia occurs in familial traits in the majority of cases *(7)*; the genetics are consistent with an autosomal dominant inheritance with variable and often no clinical effect. Neurofibromatosis, von Recklinghausen's disease, constitutes a major subgroup among children with fibromuscular dysplasia, accounting for at least 15% of all pediatric cases of renal artery stenosis *(4,8)*. Another frequent genetic cause of renal artery stenosis is Williams–Beuren syndrome *(9)*. 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 *(10)*. Apart from vascular malformation complexes, it is frequently caused by Takayasu disease, an unspecific aorto-arteriitis of autoimmune origin common in non-white populations *(11)*. Renovascular hypertension may also be due to other systemic vasculitic disorders, such as panarteriitis nodosa or scleroderma.

Renoparenchymal Disease

Hypertension is very common in various forms of glomerulonephritis. Whereas acute, e.g., post-streptococcal, 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 have 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 lead to tubulointerstitial fibrosis and tubular atrophy. Scarring processes induce local renin and angiotensin synthesis, although peripheral renin activity usually remains normal.

The underlying disease seems to be a more important determinant of hypertension than 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. 1).

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 affected by a plethora of different mechanisms in CKD *(12)*. Figure 2 gives an overview of the most important pathways involved.

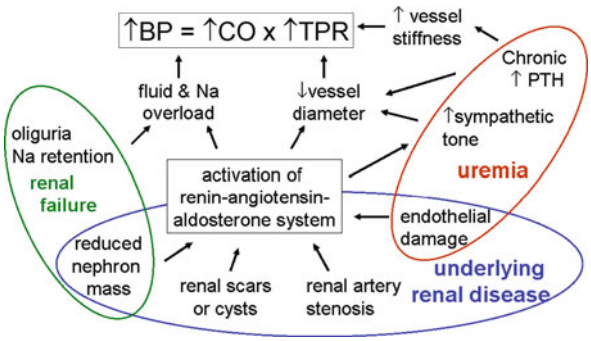

Fig. 2. Physiopathological mechanisms of hypertension in chronic kidney disease. From *(12)*, with permission.

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 *(13)*. Extracellular fluid expansion is most consistently found in hypertensive ESRD patients.

Hypertensive children on dialysis have lower residual urine output than their normotensive peers *(14)*. 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 *(15,16)* (also see Chapter 23). Plasma volume is elevated and correlated with blood pressure in renal disease, but not in essential hypertension.

On the other hand, the correlation between interdialytic weight gain and blood pressure is weak, suggesting that additional volume-independent mechanisms must affect blood pressure in CKD *(17–22)*. Also, the high prevalence of arterial hypertension in early CKD, when plasma and extracellular fluid volumes tend to be normal *(23)*, 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 independent of their saluretic effect *(24,25)*.

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 *(26)*. The removal of the native kidneys markedly reduces blood pressure and total peripheral vascular resistance, suggesting an excessive vasopressor effect of failing kidneys. Of interest, previously hypertensive, but not previously normotensive, patients respond to salt and water loading by an increase in blood pressure. Hence, the vascular tone must be affected by kidney-related as well as by kidney-unrelated mechanisms.

Renin–Angiotensin–Aldosterone System

Activation of the renin–angiotensin–aldosterone system plays a pivotal role in renal hypertension. While plasma renin activity is typically found to be 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 *(27,28)*). The infusion of normal saline fails to suppress plasma renin activity in patients with CKD stage 5 *(28)*. Hyperreninemia occurs probably due to renin secretion in poorly perfused areas, such as cysts, scars or after microangiopathic damage, or tubulointerstitial inflammation *(29,30)*, and leads to angiotensin 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 angiotensin 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-β. Moreover, in CKD renal angiotensin II upregulates afferent neuronal activity originating from the kidney, contributing to sympathetic overstimulation. Additional delayed effects of a high local angiotensin II tone include microinflammation, cardiac hypertrophy, and endothelial cell damage *(31)*; 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 *(32,33)* 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 in blood pressure *(32)*. Treatment with ACE inhibitors, but not calcium channel blockers, normalizes sympathetic activity, suggesting an effect of the renal angiotensin tone on afferent neural signaling *(33)* (Fig. 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 *(34)*. Renal denervation improves both hypertension and increased sympathetic activity *(35)*. In addition, abnormalities in dopaminergic neurotransmission and the accumulation of leptin have been postulated to be involved in CKD-associated sympathetic hyperactivation *(36,37)*. Overactivation of the sympathetic drive is also observed in renovascular and polycystic kidney disease-related hypertension *(38)*, where renal afferent nervous input is probably triggered by renal ischemia.

Recent research has suggested an important role of renalase, an amine oxidase mainly expressed by the kidneys, in the regulation of blood pressure and cardiac function *(39)*. 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 *(40,41)*.

The key vasodilatory factor secreted by the endothelium is nitric oxide (NO), the absence of which causes severe hypertension *(42)*. NO production is decreased in CKD *(43,44)* as a result of impaired biosynthesis and bioavailability of L-arginine, reduced NO synthase (NOS) expression, and increased circulating endogenous NOS inhibitors *(45)*. 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 *(43,46,47)*. ADMA independently predicts overall mortality and cardiovascular events in patients with ESRD as well as progression of CKD *(48,49)*, but these findings do not appear to be related to clinical differences in blood pressure *(50)*. A recent study in children with mild to moderate CKD showed no relationship of ADMA levels with 24-h blood pressure load *(51)*. 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 *(47)*.

Endothelin-I (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 renin–angiotensin–aldosterone system, vasopressin, and atrial natriuretic peptide and stimulates the sympathetic nervous system *(52)*. ET-1 overexpression renders mice susceptible to salt-induced hypertension and renal damage *(53)*. 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 *(54)*. Hence, circulating and possibly renal ET-1 may contribute to hypertension in CKD. Notably, ACE inhibitors reduce ET-1 expression and attenuate ET-I-induced hypertension by inhibiting the catabolism of vasodilatory kinins *(55,56)*.

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 *(57)*. In contrast, a consistent positive correlation between blood pressure and serum PTH levels is observed in patients with chronic hyperparathyroidism *(58)*. Chronically elevated PTH leads to intracellular calcium accumulation in vascular smooth muscle cells, enhancing their sensitivity to calcium and norepinephrine *(59,60)*. This effect can be blocked by calcium channel antagonists *(60)*.

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 calcium channel blockade *(61)* (Fig. 3).

Apart from PTH, cytosolic calcium is regulated by (Na,K)-ATPase. The activity of this transmembranous carrier protein is reduced in CKD by accumulation of circulating digitalis-like substances, which may contribute to the proposed cytosolic calcium-mediated hyperresponsiveness of vascular smooth muscle cells to endogenous vasoconstrictors.

Intrauterine Programming

Environmental influences in intrauterine life may predispose individuals to hypertension, dyslipidemia, and cardiovascular disease in later life. 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 *(62)*. Furthermore, intrauterine malnutrition appears to be associated with reduced nephronogenesis. 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 *(63)*, associated with marked hypertension in post-adolescent life.

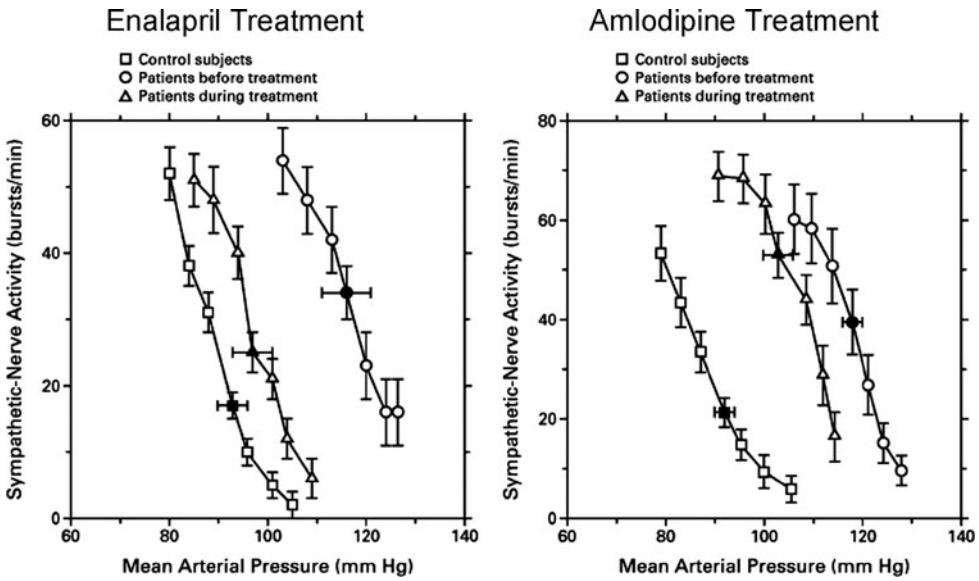

Fig. 3. Baroreflex response of sympathetic nerve activity to changes in mean arterial pressure in patients with CKD before and after 4 weeks of treatment with enalapril (n=14, *left panel*) or amlodipine (n=10, *right panel*) and in control subjects. Both drugs lowered baseline blood pressure to the same degree. Enalapril, which lowered resting sympathetic nerve activity and heart rate, shifted baroreflex curves downward and nearly normalized sympathetic nerve activity. By contrast, amlodipine increased resting muscle sympathetic nerve activity and the baroreflex response curve was shifted upward, implying that sympathetic activity remained elevated over a range of blood pressure levels. Adapted from *(33)*, with permission.

A disproportionate reduction in kidney size suggesting reduced nephron mass is evident by ultrasound in children with intrauterine growth retardation antenatally and at birth *(64,65)*. A possible link between reduced nephron endowment and the development of hypertension has been suggested by an autopsy study in subjects with essential 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 *(66)*. While this observation appears compatible with the concept of Brenner implying that a congenital reduction in nephron endowment predisposes to hypertension as a long-term consequence of glomerular hyperfiltration and glomerulosclerosis *(67)*, glomerulosclerosis was very mild in the hypertensive oligonephronic humans and absent in the sheep model *(63,66)*. Also, unilateral nephrectomy leads to hypertension only when performed during the period of active nephrogenesis in rats and sheep *(68,69)*, and children with unilateral renal agenesis have higher 24-h blood pressure than children losing one kidney shortly after birth *(70)*.

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 *(71,72)*, which may operate independently of nephron endowment. Hence, reduced renal mass and CKD may not be causally linked, but both be secondary to intrauterine malnutrition. Finally, it is possible that abnormalities in genes controlling nephron development could also affect the predisposition for hypertension *(73)*.

Pharmacological Hypertension

A number of drugs commonly administered in CKD can cause 'iatrogenic' hypertension. For example, a blood pressure elevation is commonly seen upon institution of *erythropoietin* (EPO) treatment, possibly due to arterial wall remodeling causing increased vascular resistance *(74)*. EPO may act directly on voltage-independent calcium channels on smooth muscle cells, leading to a decreased sensitivity to the vasodilatory action of nitric oxide *(75)*. Calcium channel antagonist therapy as a mechanistically logical approach for EPO-induced hypertension has been successfully tested in the rat model *(76)*.

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 angiotensin II *(77)*. 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 *(78)* have also been demonstrated after cyclosporine A treatment, especially when cyclosporine is administered intravenously. Tacrolimus appears to be somewhat less hypertensiogenic than cyclosporine A at bioequivalent doses *(79)*. Treatment with *growth hormone* leads to water and sodium retention by the distal nephron *(80)* mediated by increased intrarenal IGF-1. However, GH does not appear to increase blood pressure in children with CKD *(81)*.

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 quantitatively predicted the risk of developing end-stage renal disease; even the high-normal blood pressure range was associated with a twofold renal risk *(82)*. Numerous interventional trials have demonstrated that lowering blood pressure preserves kidney function in hypertensive patients at risk for progressive renal disease (Table 1) *(83–94,95)*.

Besides hypertension, proteinuria is a major risk factor for renal failure progression. Although hypertension aggravates proteinuria and the two risk factors are strongly interrelated in patients with CKD *(2)*, 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 *(95,96)* (Fig. 4). In the following we will discuss the pathologic mechanisms by which hypertension and proteinuria contribute to renal disease progression, and the resulting concepts of pharmacologic renoprotection in children with CKD.

Mechanisms of CKD Progression

The current concepts of the mechanisms leading to progressive renal failure are summarized in Fig. 5. 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

Table 1
Randomized Clinical Trials Demonstrating Renoprotective Effect of Antihypertensive Treatment in Adult Patients. See Text for Details

Source	*Patient population*	*Renal outcome*	*ACEI/ARB comparison vs. other AHT*	*ACEI/ARB superior*
Parving et al. *(132)*	Type 1 DM	Slowed decline in GFR	No	...
Peterson et al. *(83)*	Nondiabetic	Slowed decline in GFR	No	...
Lewis et al. *(86)*	Type 1 DM	Decreased risk for ESRD, doubling SCr, and death	Yes, ACEI	Yes
Bakris et al. *(92)*	Type 2 DM	Slowed decline in GFR	Yes, ACEI	Yes
UK Prospective Diabetes Study group *(94)*	Type 2 DM	Decreased risk of proteinuria	Yes, ACEI	No
Zucchelli et al. *(89)*	Nondiabetic renal disease	Slowed decline in GFR	Yes, ACEI	No
Hannedouche et al. *(90)*	Nondiabetic renal disease	Slowed decline in GFR	Yes, ACEI	No
Kamper et al. *(87)*	Nondiabetic renal disease	Slowed decline in GFR	Yes, ACEI	Yes
Toto et al. *(84)*	Hypertensive nephrosclerosis	Slowed decline in GFR	Yes, ACEI	No
Ihle et al. *(91)*	Nondiabetic renal disease	Slowed decline in GFR	Yes, ACEI	Yes
Maschio et al. *(85)*	Nondiabetic renal disease	Decreased risk for ESRD	Yes, ACEI	Yes
GISEN group *(93)*	Glomerulonephritis	Decreased risk for ESRD	Yes, ACEI	Yes
AASK group *(109)*	Nondiabetic renal disease	Decreased risk for ESRD, 50% GFR loss, and death	Yes, ACEI	Yes
Parving et al. *(136)*	Type 2 DM	Decreased risk of proteinuria	Yes, ARB	Yes
Lewis et al. *(137)*	Type 2 DM	Decreased risk for ESRD, doubling Scr	Yes, ARB	Yes

Table 1 (continued)

Source	*Patient population*	*Renal outcome*	*ACEI/ARB comparison vs. other AHT*	*ACEI/ARB superior*
RENAAL group *(138)*	Type 2 DM	Decreased risk for ESRD, doubling Scr	Yes, ARB	Yes
Wühl et al. *(95)*	Children with CKD	Decreased risk for ESRD, 50% GFR loss	Fixed dose ACEI in all patients; intensified BP control by non-RAS 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.

Adapted from Toto *(135)*.

to be defective in CKD *(97)*, 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 in functional renal mass leads to hyperfiltration and intraglomerular hypertension in the remaining nephrons *(67)*. The increased filtration pressure causes, or aggravates 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 angiotensin II (Ang II), endothelin-1, and others *(98)*, 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-β 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 pro-inflammatory cytokines and chemokines such as RANTES and MCP-1 and of the transcription factor NFkB *(99,100)*. 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 *(101–103)*.

Another possible mechanism of progressive renal damage has been identified in animal models of hypertensive glomerulopathy *(104)*. 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.

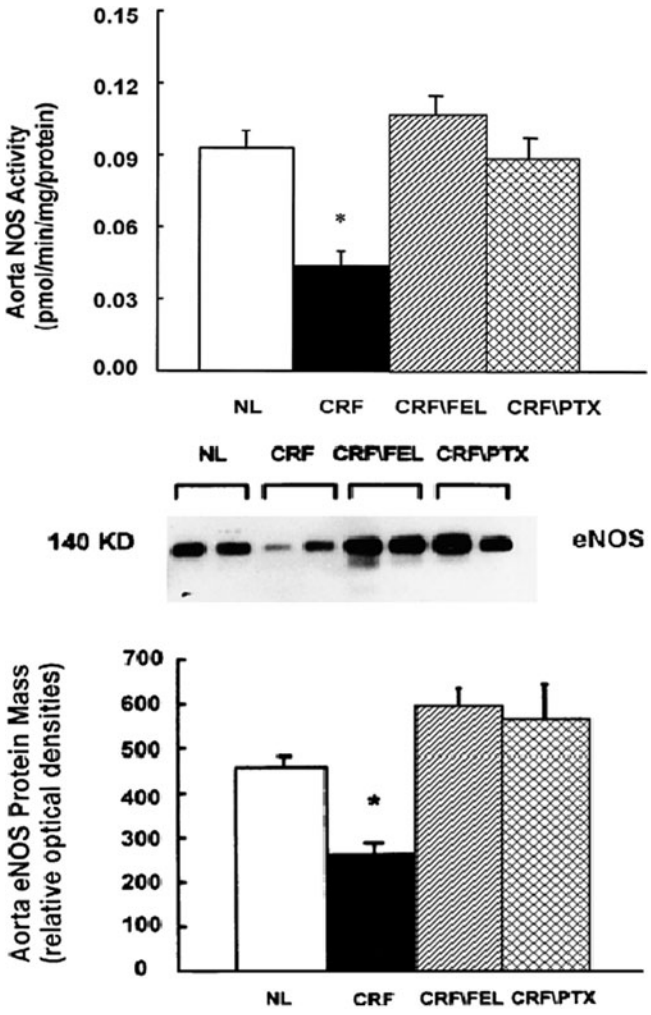

Fig. 4. Reduced NOS activity (*upper panel*) and eNOS protein expression in thoracic aorta of 5/6 nephrectomized uremic rats: NOS protein abundance and activity are restored both by calcium channel blockade (FEL, felodipine treatment) and by parathyroidectomy (PTX). From *(61)* with permission.

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 *(105)*.

Consequently, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) has recommended

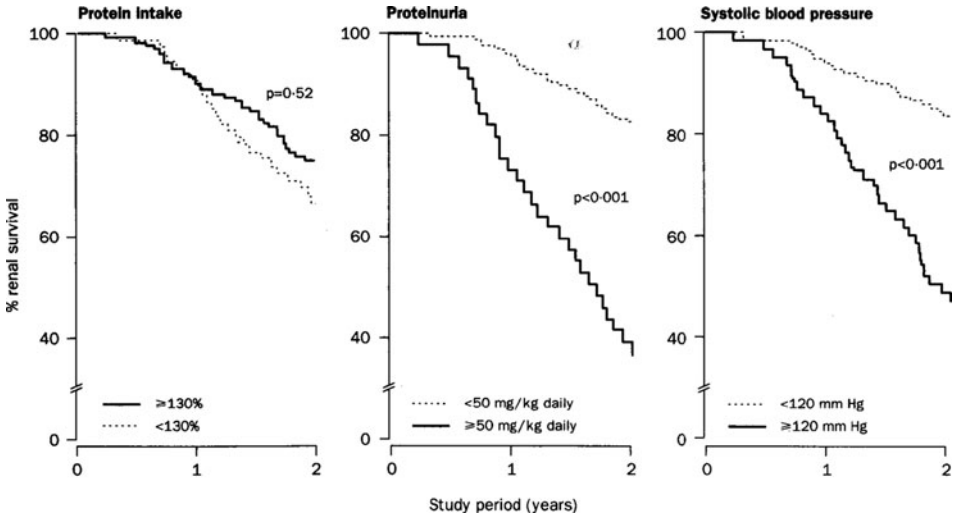

Fig. 5. Lacking effect of restricted protein intake on renal survival (defined as less than 10 ml/min/1.73 m^2 GFR loss during 2 years of observation) in 200 children with CKD (left panel). Secondary analysis revealed markedly poorer renal survival in children with proteinuria >50 mg/kg per day (middle panel) and systolic blood pressure greater than 120 mmHg. From *(96)*, with permission.

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 *(106,107)*, but 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 *(108)*. 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 *(109)*. 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 *(106–110)*.

In children with CKD, available consensus recommendations state that for children with CKD, the resting/office blood pressure target should be the 90th percentile for age, gender, and height. More recently, the Efficacy of Strict Blood Pressure Control and ACE inhibition in Renal Failure Progression in Pediatric Patients (ESCAPE) trial has provided evidence for a renoprotective effect of intensified blood pressure control based upon ambulatory BP monitoring *(95)*. Children randomized to a target 24-h mean arterial pressure 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 24-h mean arterial blood pressure between the 50th and 95th percentiles (Fig. 6). The renoprotective effect of low normal BP was independent of RAS inhibition since all subjects received the same dose of the ACE inhibitor ramipril.

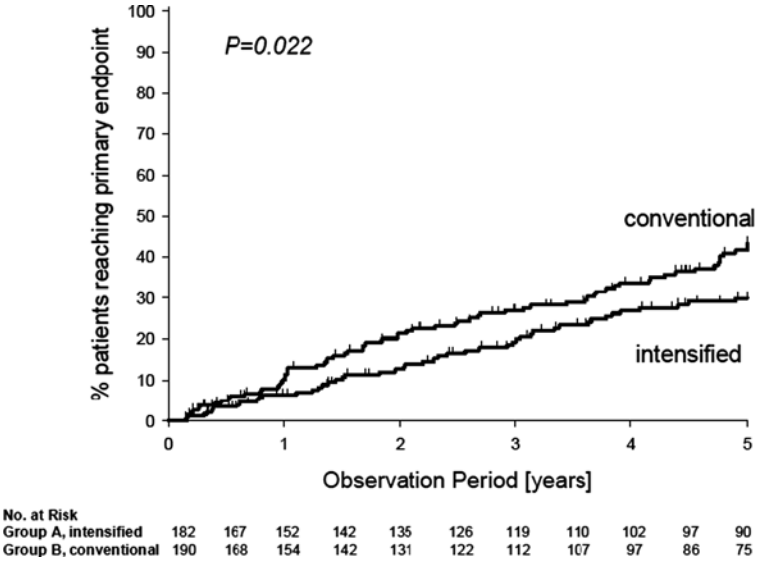

Fig. 6. Improved renal survival by intensified blood pressure control, targeting at 24-h mean arterial pressure below 50th percentile for age, sex, and height, in children with CKD (ESCAPE trial). From *(95)*, with permission.

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 24-h blood pressure exceeding the 50th percentile was associated with a compromised renal outcome (Table 2). Proteinuria was an important modifier of the renoprotective efficacy of intensified BP control. The improvement of renal survival by intensified BP control was mainly related to 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

Table 2
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 *(95)*

Achieved BP	*Below*	*Above*	*p*
25th percentile	66.3	66.8	0.63
50th percentile	73.6	57.3	0.005
75th percentile	70.1	49.9	0.001
90th percentile	70.7	29.2	<0.001
95th percentile	71.1	16.4	<0.001

linear relationship between BP reduction and LVH regression was observed *(111,112)*. 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 renin–angiotensin system (RAS) antagonists might confer specific nephroprotection beyond their antihypertensive properties. RAS 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 *(95)* (Fig. 7). To date, most albeit not all randomized clinical trials disclosed a superior renoprotective efficacy of RAS antagonists (ACE inhibitors 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 RAS antagonists, although the effect size is somewhat controversial *(113,114)*. One analysis suggested that the renoprotection conferred by ACE inhibitors may in part be independent of their antihyper and even of their anti-action *(113)*. RAS 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.

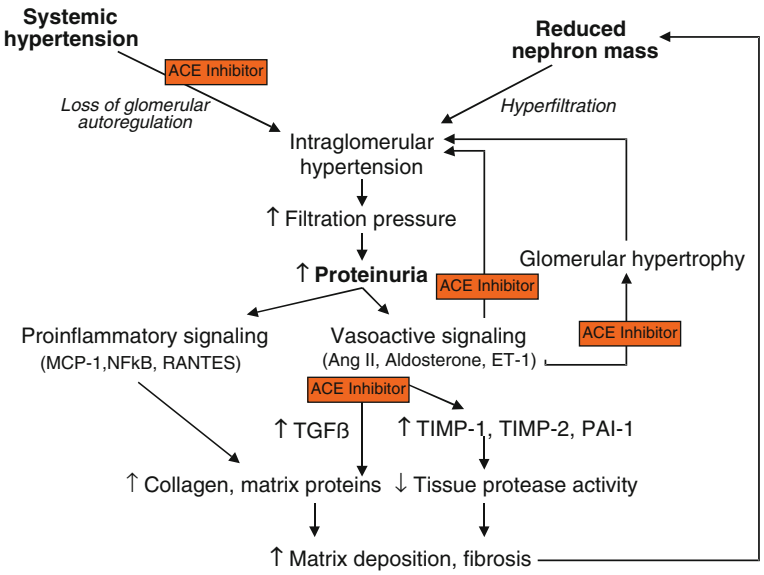

Fig. 7. Mechanisms of disease progression in CKD and sites of action of ACE inhibitors. See text for details.

Published information regarding the use of RAS 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 *(115)*, stable GFR during losartan treatment in children with proteinuric CKD *(116)*, and attenuated histologic progression in children with IgA nephropathy receiving combined RAS blockade

(117). Furthermore, the ESCAPE trial demonstrated efficient BP and short-term proteinuria reduction by the ACE inhibitor ramipril in 400 children with stages 2–4 CKD *(118)*. The drug was very well tolerated throughout 5 years of follow-up, with only 6% of patients requiring discontinuation due to acute increases in serum creatinine (n=12), hyperkalemia (n=9), or hypotensive episodes (n=2) *(95)*. 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. Hence, the nephroprotective efficacy of RAS blockade in children has not been demonstrated by the ESCAPE trial.

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 are preponderant. It could be argued that hyperfiltering nephrons in renal hypoplasia should be susceptible to the specific renal effects of RAS inhibition. Hyper- and proteinuria clearly predict CKD progression also in children *(96)*, and extensive tubulointerstitial fibrosis is commonly found in progressive pediatric nephropathies such as obstructive and refluxive nephropathies, nephronophthisis. These arguments provide a rationale for pharmacological renoprotection by RAS inhibition in children with CKD. However, individual subsets of pediatric kidney disease may remain unresponsive to RAS inhibition. Of note, polycystic kidney disease is the only disease entity identified to date in which ACE inhibition has not proven renoprotective *(119)*.

There is some evidence suggesting that the RAS is incompletely suppressed by ACE inhibition alone, and the possibility of partial secondary resistance due to compensatory upregulation of ACE-independent angiotensin II production has been suggested ('aldosterone escape') *(120–122)*. In the pediatric ESCAPE trial proteinuria was initially reduced by ACE inhibition by about 50% *(118)*. However, proteinuria subsequently gradually rebounded to pre-treatment levels within 3 years despite ongoing ramipril therapy, continued suppression of circulating ACE activity, and persistently excellent blood pressure control *(95)*. 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 RAS 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 *(123)*. 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.

Proteinuria can also be minimized by combined use of ACEIs and ARBs *(124–126)*. Whereas an earlier randomized trial had suggested improved renal survival with ACEI–ARB combination therapy *(124)*, a recent mega-trial in 28,000 patients showed no better patient or renal survival and slightly increased incidences of hyperkalemia and acute renal failure in patients on combined high-dose ramipril and telmisartan as compared to monotherapies *(127,128)*. Hyperkalemia is also the limiting factor for combinations of ACEIs with mineralocorticoid receptor blockers *(129)*.

In the ESCAPE trial, BP 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. 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 *(130)*. However, their combination with ARBs provides very powerful blood pressure lowering and even conferred a patient survival advantage as compared to the combination of ARB with thiazide diuretics (*(131)* and unpublished results of ACCOMPLISH Trial).

Non-dihydropyridine calcium channel blockers (diltiazem and verapamil) are antiproteinuric and therefore potentially renoprotective, but have a weaker effect on blood pressure *(130)*. The use of β-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 *(132)*. Newer β-blockers, e.g., carvedilol, exert a significantly greater antiproteinuric effect than atenolol at comparable blood pressure reduction *(133,134)*.

Acknowledgments

This work was supported by a grant from the KfH Foundation for Preventive Medicine.

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23 Hypertension in End-Stage Renal Disease

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Contents

INTRODUCTION

Hypertension is a frequent finding in children with end-stage renal disease (ESRD), occurring more often than in children with chronic kidney disease. The origin comes from the chronically diseased kidney (see preceding chapter), but additional risk factors appear in dialyzed and transplanted children, such as fluid overload, immunosuppressive drugs, or obesity. Hypertension 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 hypertension is one of the most important strategies in dialyzed and transplanted children to improve their survival.

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 Chapter 7) apply to children on peritoneal dialysis (PD). However, in measuring BP in children on hemodialysis (HD), the general rule to use the right upper extremity must often be disregarded if a right arm arteriovenous fistula is present because compression of the fistula may contribute to access failure. 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

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_23
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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)*. 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 *(3,4)*.

Controversies still exist surrounding the timing of BP measurement in HD patients. Casual readings are usually taken immediately after the start of 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 *(5)*. Some authors believe that postdialytic readings better reflect the interdialytic BP *(6)*, whereas others prefer predialytic BP as a guide for treatment *(7)*. A variety of influences account for these differences before, during, and after HD; changes in volume, neural signaling, local and systemic hormonal release, and vascular tone. 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 *(8)*. 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 Chapter 29) are particularly evident in ESRD patients. The white coat hypertension and white coat effect play a more minor role than in other patient groups in adults *(9)*. Conflicting data on white coat hypertension exist in dialyzed children, Koch et al. showed no white coat hypertension, whereas Lingens et al. showed 31% of dialyzed children to be reclassified as normotensive whose casual BP values were in the normotensive range *(10,11)*. 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 *(12)*. This reflects many influences that affect circadian BP patterns in dialyzed patients and that change with time (especially changes in body volume and sodium that affect nocturnal BP dip). The issue of reproducibility of nocturnal dip has not yet been studied in children. Interdialytic weight gain has been shown to correlate with ambulatory BP in children *(13)*; however, other study failed to demonstrate any correlation between interdialytic weight gain and BP *(11)*. Therefore, this issue deserves further investigation. The main advantage of ABPM, the possibility to evaluate circadian changes of BP, is particularly important in ESRD patients, in view of the prognostic significance of nocturnal dipping *(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 *(15,16)*.

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 *(11)*. Sorof et al. *(13)* 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 *(8)*.

Home Blood Pressure

Home BP performed regularly by the patients or by their parents has been shown to give lower values than clinic BP in most children *(17)*. It is an important method for control of hypertension 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 height percentile *(18)* and since available normative data for pediatric ABPM, while indexed to height in centimeters, do not exist for children with heights <120 cm *(19)*. It has been suggested that looking at norms for the age at which the child's height would fall in the 50th percentile should suffice. However, this maneuver may result in an underestimate of the normal BP range for such children. Therefore, normative data for casual BP should be taken for the 5th–95th height percentile *(18)* and normative data for ABPM for the patient's height regardless of the patient's age *(19)*.

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 prevalence of HTN in dialyzed children ranges significantly, mainly depending on the method of BP measurement and the time of the measurement. In the first weeks or months after the start of dialysis therapy, BP tends to decrease and often allows reduction in antihypertensive medication *(20)*. 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 *(21)*. An American multicenter study reported that 53% of HD and 40% of PD patients (including adolescents) received antihypertensive drugs 2 years after dialysis initiation *(22)*. Recently, the American Midwest Pediatric Nephrology Consortium Study found HTN, defined as mean casual BP ≥95th percentile, in 59% of HD children *(23)*. Similar observations were reported by the Mid-European Pediatric Peritoneal Dialysis Study Group, by the North American Pediatric Renal Transplant Cooperative Study, or by the nationwide survey in Poland *(24–26)*. These multicenter studies were based on casual BP measurements.

Using ABPM, which provides a more detailed analysis, Lingens et al. *(11)* 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 *(13)*, but in discordance with the finding of Lingens et al. who found no correlation between these parameters *(11)*.

An attenuated nocturnal dip in BP 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 *(27,28)*. In the study by Lingens et al. *(11)*, 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, respectively, which is lower than in healthy children. In the Finnish investigation, a decreased nocturnal decline (non-dipping, defined as nighttime BP decrease <10%) was noted in 40% of children on PD *(29)*.

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. *(30)*. Diminished glomerular filtration rate and sodium excretory capacity result in water and sodium retention in the body, 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 *(31)*. After the disappearance of edema, HTN may persist until strict control of hypervolemia, e.g., by extension of the dialysis time, and may finally reduce BP *(32)*. However, hypervolemia may also occur in the absence of HTN.

Increased peripheral vascular resistance caused by humoral factors inappropriate to the volume state is another explanation of HTN in dialyzed patients *(33)*. Activation of the renin–angiotensin–aldosterone system (RAAS) was demonstrated by high plasma renin activity *(34)* in adult patients on HD treatment *(35)*. 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 *(36)*. In children, a two- to fourfold increase in plasma noradrenalin and adrenalin levels was noted during an HD session *(34)*. Sympathetic overactivity appears to be mediated by an afferent signal arising in the failing kidney and HD patients who had undergone bilateral nephrectomy display normalization of the sympathetic activity *(37)*. The finding of structural abnormalities of coronary and great arteries in experimental CRF 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 *(38)*.

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 *(39)*. Endothelium-dependent vasodilatation has been reported to be impaired in uremia, reflected by reduced release or action of nitric oxide (NO) *(40)*, 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 *(41,42)*.

Finally, HTN in ESRD is related to the duration of HTN in the predialysis period and, therefore, to the original renal disease and chronic vascular changes (i.e., the Folkow hypothesis) as well as to declining residual renal function during dialysis *(43)*. 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 possibly also modify cardiovascular risk. Potential risk factors responsible for the development of HTN in dialyzed children are summarized in Table 1.

Table 1
Causes of Hypertension in Dialysed Children

Extracellular volume overload and sodium retention
Inappropriate high renin–angiotensin 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, increased renin secretion, and sympathetic activity)
Genetic factors
Iatrogenic factors (e.g., rh-EPO, steroids 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 concern different organs. Before efficient antihypertensive therapy became available, involvement of the central nervous system was one of the most frightening manifestations of severe HTN in children with ESRD *(44)*. The kidneys may be damaged further by elevated BP—residual renal function may be compromised by 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 *(45)* and normal LV contractility *(46)*. However, LV diastolic dysfunction occurs in about half of the adult dialysis patients and has also been demonstrated in children *(47)*.

Four main structural abnormalities of the heart have been described in adult patients with CRF and ESRD with or without HTN *(38)*: (1) LV hypertrophy (LVH); (2) expansion of the nonvascular cardiac interstitium leading to intracardial fibrosis; (3) changes of the vascular architecture (thickening of intramyocardial arterioles and reduction of capillary length density); and (4) myocardial calcification. LVH is most relevant cardiac abnormality in children with ESRD.

LVH is a strong and independent predictor of death and cardiac failure in adult dialysis patients *(48)*. Risk main 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 *(49)*: 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) and eccentric (or asymmetric) LVH caused mainly by volume overload, resulting primarily in dilatation of the LV chamber (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 cases *(50,51)*. On the contrary, the third abnormal finding of the cardiac geometry found on the echocardiography, namely concentric remodeling (i.e., increased RWT but normal LVM), is only rarely seen in pediatric ESRD patients *(51)*.

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 *(48)*. Reduced diastolic filling is closely associated with LVH and increased stiffness of the LV chamber owing to collagen accumulation.

Many reports have described LVH in children with ESRD *(45)*. 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 as a LVMI greater than the 95th percentile for normal children and adolescents *(52)*.

In the largest echocardiographic study reported in children with ESRD (aged <15 years), 51% of patients on HD and 29% on PD exhibited LVH. However, no methodological details were collected in this European ERA/EDTA pediatric registry *(21)*. 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. *(50)*, 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), 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.

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%, *(53)*). Similarly, the Finnish study has demonstrated only 45% of PD children to have LVH that highly correlated with the severity of HTN (pressure overload) and ANP level, a marker of hypervolemia *(29)*. On the contrary, the results from a German study showed similar LV mass index with both modes of treatment *(45)*. 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 *(54)*. Such regression of LV mass is associated with better survival *(55)*. In adults, LV mass may also decrease after conversion from conventional to daily nighttime HD, associated with a drop of BP *(56)*. In children, only very few studies have 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 *(51)*. 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 *(57)*. The reduction of LVH was associated with the 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 *(38)*. 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 *(58,59)*. Histologic examination 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. The most 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 *(60)*. 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 hypertension may be the priority for preventing or improving cardiovascular damage in these patients.

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 of systolic BP and diastolic BP) *(61,62)*. Long-term studies have demonstrated that adequate BP control improves the survival of adult ESRD patients *(63)*.

Since the start of the dialysis era, there has been a remarkable decrease in early cardiovascular mortality in children and adolescents with ESRD *(64,65)*. 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 0.1 in healthy children, i.e., 1000 times less than in ESRD children), rising to 2.3 for all patients reaching the age of 20–30 years *(66)*. According to this study, cardiovascular mortality corresponds to approximately 20–30% of all deaths encountered in dialyzed children and young adults up to 30 years.

It should be stressed that late fatal cardiovascular events, such as myocardial infarction and cerebrovascular accidents, are the result of both specific (uremic) and unspecific (traditional atherosclerotic) risk factors. However, because the cardiovascular mortality in children with ESRD is up to 1000 times higher than in healthy children, mainly the disease-specific—uremic—risk factors are responsible for such a tremendous increased mortality in ESRD children.

A more detailed study from the Netherland 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 population of same-aged children *(65)*. 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 spending on dialysis (i.e., early transplantation,

seven times lower risk of death in transplanted than in dialyzed children) and rigorous treatment of hypertension (threefold increased risk of death in hypertensive children).

Evaluation of Hypertensive Children on Dialysis

Every pediatric patient with ESRD should be regarded as potentially hypertensive (due to the very high prevalence of hypertension including nighttime 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 HTN in ESRD"). ABPM is especially helpful in HD patients, because it allows a better recognition of intra- and postdialytic (particular nocturnal) BP changes when continued over 24 or 48 h *(14)*. It is also a useful method for evaluation of BP rhythms in children on PD. 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, is required, even in the absence of any clinical signs of cardiovascular disease *(45)*. There is no doubt that the collaboration of the nephrologist with and 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 *(60)*. 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.

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 *(67)*, sonography of the inferior vena cava diameter *(68)*, and determination of the ANP in plasma *(29)*. 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 *(6)*. A new technique that can help in assessment of child's dry weight is noninvasive monitoring of the hematocrit in HD patients. This method has recently been studied also in pediatric HD patients *(69)*.

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 *(33)* 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 *(70)*. 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 extracted *(71)*. 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 help to decrease thirst). During this period the true "dry weight" should become evident (see "Evaluation"). Noninvasive monitoring of hematocrit, if available, may facilitate accurate establishment of dry weight *(69)*. In some patients (especially without severe HTN before initiation of dialysis), normal normalization of HTN 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 to 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 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 (six times 2 h/week over 6 months) were able to reduce extracellular water, mean 24-h BP, and LV mass significantly, compared with conventional HD (three times 4 h/week), and antihypertensive medication was able to be stopped or lowered in most subjects *(72)*. Most recently, similar study has been performed also in children in which after a 16-week study with frequent HD (six times/week) the patients exhibited progressive reduction in casual predialysis BP, discontinuation of antihypertensive medication, and decreased BP load by ABPM *(73)*. Similar results were obtained in adult patients switched from conventional to nocturnal dialysis *(56)*. In other studies, reduction of predialysis BP was obtained by gradually lowering the dialysate sodium content during HD sessions *(74)*. 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 procedure to minimize hypotensive episode and to be able to reach the true dry weight. Another measure how to improve BP control in dialyzed children and to reduce dialysis-associated events is 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 *(69)*.

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 a less stringent dialytic volume control. 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 *(75)*. 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. It can be obtained by dietary, dialysis, or pharmacological measures. Salt-restricted diet (<6 g/day) has been shown to reduce peripheral vascular resistance and BP in adult patients *(76)*. However, the compliance with the sodium-restricted diet is low, especially if it has to be combined with fluid restrictions. No pediatric data are available on the effect of salt-restricted diet on BP in ESRD patients. Dialysis regimen with low-sodium dialysate

fluid concentration (135–136 mmol/l) can reduce BP in adult patients *(77)*. Similar effect is expected also 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; however, it is not possible to use them in anuric or severely oliguric patients.

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 dry weight. Since no controlled studies have been performed in this group of patients, the optimal drug therapy remains empiric, based on the 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 *(21)*. In the recent nationwide survey in Poland, ACE inhibitors and CCBs were given to 50 and 46% of dialyzed children, respectively *(26)*. 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 Chapter 31).

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 *(78)*. However, some trials showed important BP differences between investigated groups of patients and are therefore partly inconclusive whether ACE inhibitors and ARBs have cardioprotective effects beyond their BP-lowering effects. 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 contribute to improved survival *(62)*. 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 *(26)*. 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% *(26)*. 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.

HYPERTENSION IN CHILDREN AFTER RENAL TRANSPLANTATION

Introduction

Hypertension is a common and serious complication in patients after renal transplantation *(79,80)*. It is an important risk factor for cardiovascular morbidity and mortality in transplanted patients *(81)*. Furthermore, it is a strong risk factor for impaired graft survival in adult and pediatric patients *(82–84)*.

Measurement of BP in Transplanted Children

Casual blood pressure 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 hypertension nor measure BP during sleep. 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 *(83)*. The main reasons are the ability of ABPM to reveal white coat hypertension 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 *(85)* and the ability to diagnose masked hypertension (i.e., normal casual BP but increased ambulatory daytime BP) in children with ESRD and after transplantation. Finally, the results of ABPM are more closely related to renal function in transplanted patients than the results of casual BP *(86)*. Therefore, regular use of ABPM is recommended in all patients after renal transplantation regardless of the values of casual BP. How frequently ABPM should be used in transplanted children is not clear; however, it is evident from the superiority of ABPM over CBP that ABPM should be performed at least once a year in every transplanted child and at least 6 months after every change in antihypertensive therapy.

An interesting finding of several studies *(87,88)* is the predominance of nighttime hypertension in these patients. This finding further stresses the importance of ABPM with its monitoring of BP values during the night that are usually elevated in hypertensive transplanted children.

Reduced physiological decrease of BP during the night (nocturnal dip) has been revealed in 30–72% of transplanted children *(87,88)*. Adult transplant patients who are non-dippers have greater left ventricular mass than dippers *(89)*. 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 *(88)*.

Home BP self-measurement is also an important method for measurement of BP. It is increasingly used as a valuable supplement to casual BP and also ABPM in children with chronic renal failure or on renal replacement therapy *(17)*. It is especially recommended in children receiving antihypertensive medication.

Definition and Prevalence of Hypertension in Transplanted Children

The same definition is used for transplanted children as for healthy children or children on dialysis. The prevalence of hypertension in children after renal transplantation ranges considerably between 58 and 89% *(79,80,87,88)*. The reason for the wide range in the prevalence of hypertension is based mainly on the different methods of BP measurement and different definitions of hypertension in various trials. Studies using casual BP measurements always report lower prevalence of hypertension 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 *(90)*. Moreover, children should be defined as hypertensive on the basis of two criteria—use of antihypertensive drugs and current BP level, and control of hypertension should also be assessed according to these criteria. Children on antihypertensive drugs with normal current BP level should be regarded as having *controlled* hypertension and children on antihypertensive drugs with elevated current BP level should be regarded as having *uncontrolled* hypertension. The main reason for this differentiation is the fact that it has been shown in several trials that transplanted patients with controlled hypertension have the same graft survival as spontaneous normotensive patients (i.e., normal BP without antihypertensive drugs). In contrast, patients with uncontrolled hypertension have significantly worse graft survival *(84,91)*. Therefore, using only one category of hypertension (regardless of the therapeutic control of hypertension) or antihypertensive drugs as the only criterion for definition of hypertension 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 post-transplant hypertension is multifactorial *(79,80,92)*. The main causes are summarized in Table 2. Hypertension prior to transplantation caused mainly by the diseased native kidney is believed to be a significant risk factor for the presence of hypertension after successful renal transplantation *(99,92)*.

Table 2
Causes of Hypertension in Transplanted Children

Recipient's native kidney
Immunosuppresive drugs (steroids, cyclosporine A, tacrolimus)
Graft dysfunction (acute rejection, chronic allograft nephropathy—dysfunction)
Kidney from cadaveric, borderline, or hypertensive donor
Renal graft artery stenosis
Overweight/excessive post-transplant weight gain
Genetic factors (primary hypertension, genes of RAAS)
Recurrent or de novo renal disease
Others (e.g., polycythemia, pyelonephritis, ureteric obstruction, lymphocele)

Children receiving kidneys from deceased donors are more frequently hypertensive than children receiving grafts from living donors *(80,92)*. The lower prevalence of hypertension among children after living donor transplantation could be one of the reasons for better graft survival of the living donor grafts in comparison with cadaver. This hypothesis is supported by the results of a single center study which shows that post-transplant hypertension is, together with episodes of acute rejection, the only independent determinant of graft survival in children after living donor transplantation *(93)*.

Steroids are well-known risk factor for post-transplant hypertension. Several factors, such as sodium retention or increase in cardiac output and renal vascular resistance, induce steroid-related hypertension. Elimination of steroids in stable patients showed reduction of BP in adult as well as in pediatric patients *(94,95)*, and children with steroid avoidance immunosuppressive protocol showed improvement in hypertension *(96)*. In a cross-sectional study the patients on alternate dose steroid treatment showed significantly lower prevalence of hypertension than children on daily steroid medication *(88)* and other studies showed that conversion from daily to alternate dose steroid therapy significantly reduces BP *(97)*. Therefore, adoption of steroid-sparing or steroid-free immunosuppression regimens can be considered as a treatment strategy for improving control of BP in transplanted children.

With the introduction of the calcineurin inhibitor cyclosporine, there has been a dramatic increase in the prevalence of post-transplant hypertension *(92)*. Hypertension induced by cyclosporine is caused by several mechanisms *(98)*. Gordjani et al. *(92)* 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 hypertension 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 hypertension between children treated with cyclosporine and those with tacrolimus *(99)*. New immunosuppressive agents such as mycophenolate mofetil, sirolimus, or everolimus do not have BP increasing effects, and therefore their use is a further option to improve the control of hypertension in transplanted children *(98)*.

Renal graft dysfunction is another risk factor for post-transplant hypertension; 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 hypertension *(86,91,100)*. 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 *(84)*. However, hypertensive children had poor allograft function (glomerular filtration rate GFR <50 ml/min/1.73 m^2) more frequently than normotensive patients, whereas children with normal BP more frequently had normal graft function (GFR >75 ml/min/1.73 m^2).

Current body weight or change of body weight is a well-known and potent determinant of BP level in adults and children *(101)* and most children gain weight after renal transplantation *(102)*. 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 hypertension with current surgical technique using aortic patches *(103)*. Doppler ultrasonography, magnetic resonance angiography, and spiral CT angiography are noninvasive techniques that can be used to identify this; however, in some cases, a traditional arteriogram may need to be performed. 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 may be associated with the occurrence of hypertension, although these conditions are not common causes of significant post-transplant hypertension.

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. *(82)* 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 *(81,84)*. The results from the NAPRTCS registry showed that the use of antihypertensive medication, a definition for hypertension in this retrospective analysis, is associated with higher graft failure *(80)*. Increased BP is therefore clearly associated with decreased graft survival. Despite these clear findings, it is still a matter of debate whether post-transplant hypertension 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. *(84)* showing that hypertension is associated

with allograft failure in children with normal graft function but not in children with severely impaired graft function suggest that hypertension is not only a marker of graft dysfunction but also a direct cause of renal graft damage (Fig. 1).

Similar to the general population, hypertension is associated with increased cardiovascular morbidity also in the population of 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% children *(87,88)*. Matteucci et al. *(104)* found a correlation between left ventricular mass index (LVMI) and mean 24-h systolic BP; however, another study done by Morgan et al. *(87)* could not find any relationship between LVMI and ambulatory BP data. However, in a recent study, Kitzmueller et al. found a correlation between LVMI and ABPM data at repeated measurement but not at baseline suggesting that control of BP, i.e., change of BP level during longitudinal follow-up, is important for the maintenance of the myocardial architecture *(105)*.

Hypertension is also a risk factor for increased cardiovascular mortality seen in transplanted adult patients *(106)*. Similar studies in children are rare. The Dutch Cohort Study has demonstrated that hypertension is one of the most powerful risk factor for cardiovascular morbidity and mortality also in children after renal transplantation *(65)*. 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.

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 (at least once a year). The diagnostic evaluation of hypertension in transplanted children should consider the multiple etiologies of post-transplant HTN (Table 2). Echocardiography should be assessed at least once a year to determine the presence or absence of hypertensive target-organ damage on the heart.

Treatment of Hypertensive Children After Renal Transplantation

There is clear evidence from the observational studies on the correlation between BP and cardiovascular morbidity, mortality, and graft function that post-transplant hypertension must be treated at least as it is in the general pediatric population or in children with chronic kidney disease. If an identified treatable cause of hypertension 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 hypertension in children after renal hypertension are less clear or even controversial. 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 post-transplant hypertension because they counteract the afferent arteriolar vasoconstriction caused by calcineurin inhibitors and reduce their nephrotoxicity *(107)*.

There has been some concern that angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs) may deteriorate graft function in case of undiagnosed graft artery stenosis or due to the preferential efferent arteriolar vasodilation and reduction of intraglomerular pressure. However, it has been demonstrated that ACE inhibitors are safe and effective drugs in adult as well as pediatric transplant patients *(108,109)*. Furthermore, ACE inhibitors and ARBs can slow the progression of chronic native kidney diseases in adults mainly by long-term reduction of intraglomerular pressure. The data on the renoprotective ability of ACE inhibitors in children are still lacking. The

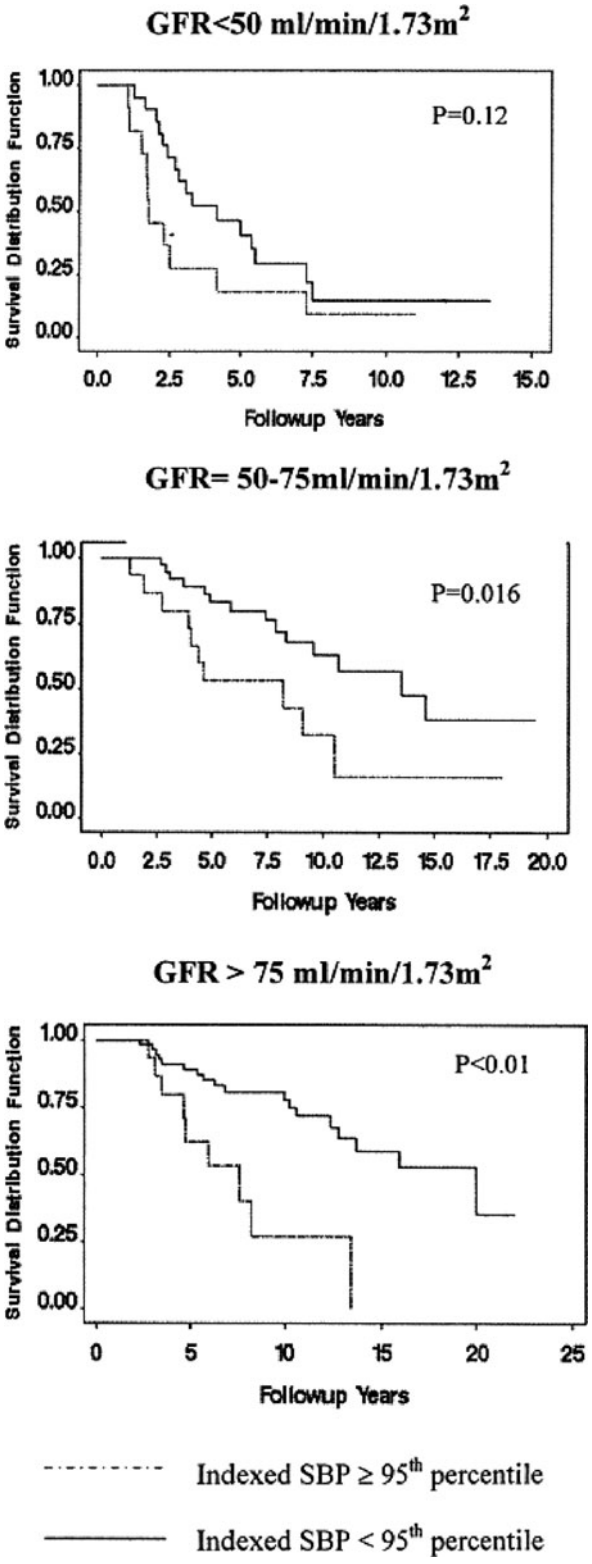

Fig. 1. Renal allograft survival by 1-year indexed systolic BP and 1-year graft function (reprinted from Mitsnefes et al. *(84)*, figure 2).

ability of ACE inhibitors to slow the progression of chronic allograft nephropathy (CAN), 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 CAN *(109,110)*. However, the results from CTS published recently did not show any improvement of patient or graft survival in patients treated with ACE inhibitors *(111)*. Therefore, this issue is still controversial and needs prospective interventional trials to resolve this controversy. At present, there are no data on the use of angiotensin receptor blockers (ARBs) in children after renal transplantation. However, in adults, there are several small single center studies showing that ARB can also be used in transplanted patients *(112)*.

Beta-blockers are also effective drugs in transplanted patients *(113)*. 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 four major classes of antihypertensive drugs can therefore be used in transplanted patients. Post-transplant hypertension 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 other in renal transplant recipients *(107)*. In most pediatric renal transplantation centers, the most commonly used antihypertensive drugs are CCB, which are given to 38–65% of transplanted children *(87,88,90)*. The second most commonly prescribed drugs are ACE inhibitors and beta-blockers. Diuretics are given less frequently to transplanted children.

Non-pharmacological lifestyle measures (reduction of increased body weight, reduction of salt intake, and physical activity) should be encouraged even during antihypertensive drug therapy as they target the risk factors not only for hypertension but also for cardiovascular morbidity and mortality of the patients (obesity, increased salt intake, and 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 hypertension in patients with diabetic nephropathy *(114)*. However, there are no prospective interventional trials showing that target BP lower than the conventional cutoff of 140/90 will improve graft function and long-term graft survival. The same is true also for pediatric renal transplant recipients. The results of a most recent large European multicenter study (ESCAPE trial) showed that reduction of ambulatory 24-h BP <50th percentile leads to significantly slower progression of chronic renal insufficiency in children comparing to children with BP between 50th and 95th percentile *(115)*. However, it is not known whether these results can be extrapolated to transplanted children. The current recommendation of the Fourth report of the National High BP Education Program Working Group on High BP in Children recommends target BP <90th percentile for children with chronic kidney diseases *(18)*.

While no such recommendation has yet been made for the management of hypertension after renal transplantation, adoption of this target would seem logical *(116)*.

The control of hypertension in children after transplantation is still not adequate. Only a minority of children treated for hypertension after kidney transplantation has BP at least below the target BP level recommended for the healthy population, i.e., <95th percentile *(88)*. The prevalence of persistent hypertension despite antihypertensive treatment (i.e., prevalence of uncontrolled hypertension) ranged between 45 and 82% in the recent pediatric studies using ABPM *(87,88)*. This means that only 18–55% of children after renal transplantation had hypertension controlled by drugs with BP at least <95th percentile. These data suggest that there is a high potential for improvement of antihypertensive therapy in children after renal transplantation.

The reasons for the insufficient antihypertensive therapy in transplanted patients have not been thoroughly investigated. Many factors, such as chronic allograft dysfunction, need for lifelong use of blood pressure elevating immunosuppressive drugs (steroids, cyclosporine, and tacrolimus), obesity, salt retention, renin secretion from diseased native kidneys, and the fear of ACE inhibitors in transplanted patients are discussed as the major reasons for inadequate BP control in transplanted patients. Last, noncompliance can play an important role in the control of hypertension, particularly in adolescent patients. Therefore, adherence to the recommended antihypertensive drugs should be checked during every outpatient visit.

An important issue is whether the poor control of hypertension can be improved and whether improved control of hypertension can stabilize or even improve graft function or cardiac complications. Results from CTS group showed in adults that improved control of BP is associated with improved long-term graft and patient survival *(117)*. Two recent studies have demonstrated promising result on this issue also in children. In a prospective interventional trial on intensified treatment of hypertension, 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. 2) *(118)*. In the second most recent study, left ventricular

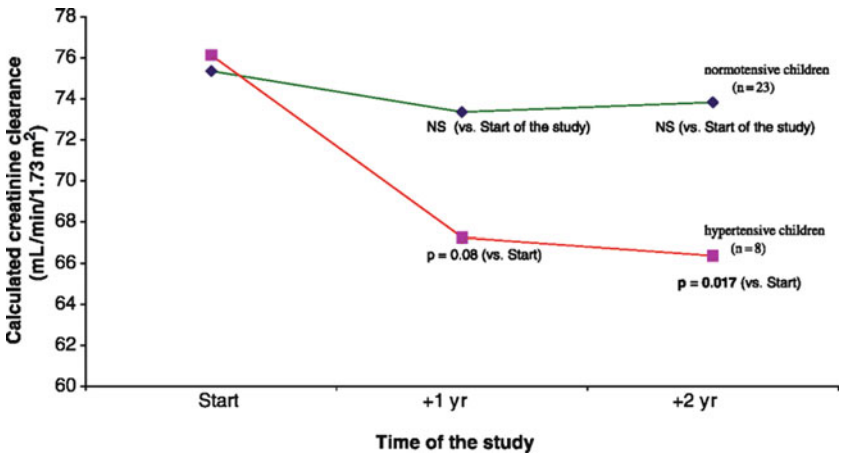

Fig. 2. Graft function in children being normotensive and hypertensive at 2 years during 2-year interventional study (reprinted from Seeman et al. *(118)*, figure 3).

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 of cardiac structure were associated with decrease of systolic and diastolic BP index *(119)*.

Acknowledgments

Supported by the Ministry of Education of the Czech Republic VZ MŠMT No 0021620819 and Ministry of Health VZ MZ No 0006420301, MZOFNM2005.

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24 Sequelae of Hypertension in Children and Adolescents

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Contents

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 USA *(2)*. Moreover, hypertension 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 account for 8% of annual US healthcare costs at more than 20 billion dollars *(3)*. There is also increasing evidence that the pathogenesis of hypertension begins in childhood, and hypertension in children is a risk factor for development of adult cardiovascular disease *(4,5)*. However, hypertension in children is often underdiagnosed, and the alterations in end-organ structure and function noted in adult hypertensive patients begin in childhood *(6,7)*. 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, prompt recognition of these alterations in children and adolescents may prevent future morbidity and mortality in these patients *(8)*.

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_24
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SEQUELAE OF CHRONIC HYPERTENSION

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 lifestyle. Croix and Feig *(9)* recently 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 *(9)*. 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 *(9)*. 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 1).

Table 1
End-Organ Alterations in Pediatric Patients with Chronic Hypertension

Cardiac structure
Increased left atrial size
Left ventricular hypertrophy
Cardiac function
Diastolic dysfunction
Vascular structure
Increased cIMT
Arterial stiffening
Atheromatous changes
Renal function
Microalbuminuria
Retinal vasculature
Arteriolar narrowing
Tortuosity
AV nicking
Cognition
Short-term memory
Attention/concentration

Cardiac Structure and Function

Hypertension is a major risk factor for development of congestive heart failure, and randomized controlled trials have demonstrated a consistent decrease in risk for development of congestive heart failure upon lowering of elevated blood pressure in adults *(10,11)*. In the classical paradigm for the pathogenesis of hypertensive heart disease, development of LV failure is preceded by alterations in both left atrial and ventricular geometry *(12)*. The changes in ventricular geometry occur in two different patterns *(12)*. In concentric

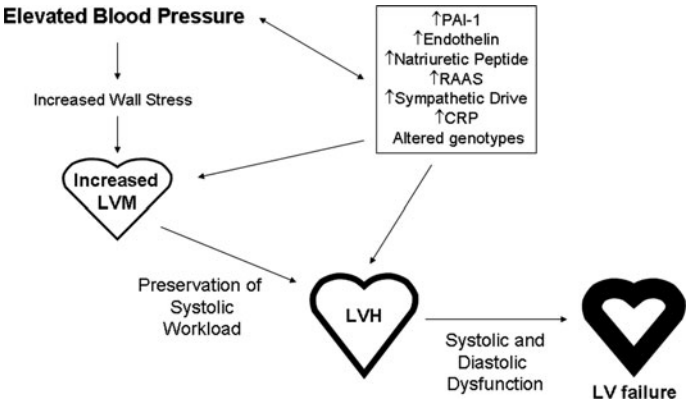

Fig. 1. Pathogenesis of left ventricular hypertrophy in pediatric patients with chronic hypertension. Renin–angiotensin–aldosterone axis (RAAS), left ventricular mass (LVM), left ventricular hypertrophy (LVH), C-reactive protein (CRP), plasminogen activator inhibitor-1 (PAI-1).

LV hypertrophy, parallel addition of sarcomeres causes an increase in the cross-sectional area and diameter of the cardiac myocytes *(13)*. These alterations lead to a significant increase in LV wall thickness out of proportion to an increase in size of the LV cavity *(13)*. In contrast, a symmetric increase in wall thickness as well as LV cavity size results in eccentric LVH as a result of sarcomere addition in series. Hypertension is generally associated with development of concentric hypertrophy as increased blood pressure and pulse pressure oppose LV ejection inducing increased LV wall stress (Fig. 1) *(14)*. 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 (Fig. 1) *(15–19)*. Recently, a central role for the renin–angiotensin–aldosterone axis (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 *(20)*. The investigators found that the aldosterone–renin ratio alone was significantly associated with development of both concentric and eccentric remodeling *(20)*. 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 (Fig. 1) *(15)*. 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 (Fig. 1) *(15)*. Furthermore, abnormalities in myocardial electrical conduction in the hypertrophied muscle also trigger the development of arrhythmias.

In terms of atrial structure, left atrial enlargement is associated with duration of elevated blood pressure, the levels of sustained systolic blood pressure, and pulse pressure in the general adult population *(21)*. However, only age, race, and obesity were significant predictors of left atrial size in hypertensive adults *(22)*. Although 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 *(23)*. Although data are limited in the pediatric population, Daniels et al. *(24)* studied a cohort of 112 pediatric patients with hypertension and found that 51% of patients had

left atrial dimensions above the 95% upper confidence limit. In statistical analysis, height, body mass index, and systolic blood pressure were independent predictors for left atrial enlargement *(24)*. 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 *(24)*. 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 mass *(24)*. The prognostic value of these findings in pediatric patients remains to be determined.

Left ventricular hypertrophy is a frequent finding in adults with hypertension. Data from several studies have suggested that the prevalence of left ventricular hypertrophy in hypertensive adults ranges from 33 to 81% *(25,26)*. More importantly, LVH has been noted to be a risk factor for cardiovascular disease, cardiovascular morbidity, ventricular arrhythmias, and cardiovascular death *(27,28)*. Abnormalities in left ventricular structure are also present in 40% of children and adolescents with hypertension *(29,30)*. A recent retrospective analysis demonstrated that the prevalence of LVH increased with severity of hypertension. Specifically, patients with normal blood pressures were noted to have a prevalence of LVH of 5.7%, whereas patients with stage 1 hypertension had a prevalence of 18% compared to 32% in patients with stage 2 hypertension *(31)*. 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 *(32)*. In this study, children with LVH were more likely to have a higher BMI and to be non-white compared to those without LVH. Surprisingly, after controlling for age, sex, and height, no associations between blood pressure parameters at the initial visit and LVH were detected *(32)*. In contrast, Richey et al. *(33)* detected associations between development of LVH and systolic blood pressure as well as 24-h systolic blood pressure load. In addition, LVM has correlated with serum uric acid and homocysteine levels *(30)*.

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 *(34)*. Similar findings have been reported in pediatric patients with hypertension *(35,36)*. Recently, Border et al. *(37)* compared the ventricular function of 50 pediatric patients with essential 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 *(37)*. 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 *(37)*. When compared to the controls, 39% of hypertensive patients demonstrated abnormal left ventricular compliance similar to adult studies *(37)*. 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 *(37)*.

Vascular Structure

In parallel with cardiac abnormalities, hypertension induces alterations in the structure and function of the arterial tree *(38)*. The mechanisms underlying these changes are multifactorial and incompletely understood (Fig. 2) *(39,40)*. Increased pulse pressure in

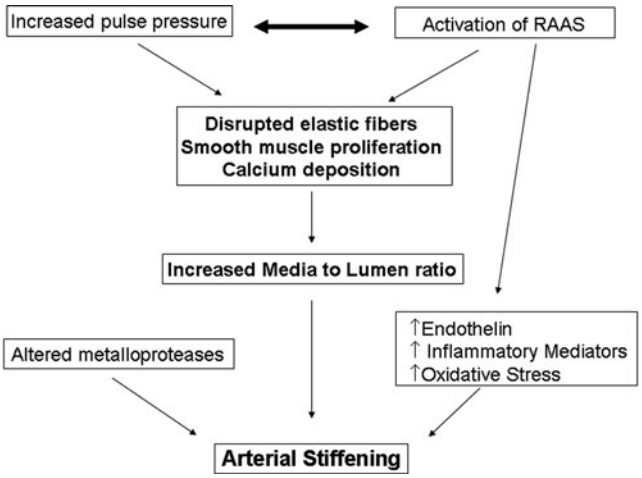

Fig. 2. Vascular adaptation in pediatric patients with chronic hypertension. Renin–angiotensin–aldosterone axis (RAAS).

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 (Fig. 2) *(39)*. Because elastin influences smooth muscle proliferation and migration, this redistribution of elastin fibers leads to dedifferentiation of smooth muscle cells and arterial wall hypertrophy (Fig. 2) *(40)*. Mechanical stress also alters the activity of matrix metalloproteinases which are essential for maintenance of the extracellular matrix of the arterial wall (Fig. 2) *(39)*. Continued wall stress enhances production of endothelin, a potent vasoconstrictor which when combined with other inflammatory mediators contributes to significant endothelial dysfunction (Fig. 2). Ultimately, these changes lead to structural reduction of the arterial lumen diameter and increased arterial stiffness (Fig. 2) *(39)*.

To evaluate these alterations, vascular ultrasound has emerged as a noninvasive means to assess changes in vascular structure and risk of future cardiovascular events *(41)*. 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 *(41)*. In a study of 32 patients referred to a pediatric hypertension clinic, 28% of patients demonstrated increased cIMT *(42)*. 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 *(42)*. Similarly, in the Bogalusa Heart Study, office-based systolic and diastolic blood pressures in childhood did not predict cIMT in adulthood *(43)*. Lande et al. *(44)* 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 *(44)*. 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 *(44)*. In contrast, associations between office-based blood pressure measurements and cIMT were not detected *(44)*. These findings validated previous reports

that alterations in the vascular tree occur in childhood and correlate with blood pressure load as assessed by ABPM.

In addition to cIMT, pulse wave velocity is a widely used noninvasive method to assess arterial stiffness *(45)*. 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 *(45)*. 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 *(46)*. A recent report demonstrated that pulse wave velocity is increased in hypertensive adolescents compared to normotensive controls *(47)*. In a separate report, elevated mean blood pressure independently predicted elevated pulse wave velocity in a larger cross-sectional study of over 200 adolescents *(48)*. 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 3000 accident victims aged 15–34 years who underwent autopsy *(49)*. In their analysis, hypertension significantly augmented the risk for development of atherosclerosis in the cerebral arteries *(49)*. In a separate follow-up study, hypertension also enhanced formation of raised lesions from fatty streaks in the abdominal aortas *(50)*. Interestingly, this association was only observed in African-American subjects and not in white subjects *(49,50)*. However, the PDAY study used the intimal thickness of the renal arteries as a surrogate marker for blood pressure which may confound the association *(51)*. 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 *(52,53)*. Together, these studies suggest that elevated blood pressure contributes to both initiation and progression of atherosclerosis.

The Kidneys

Hypertension is the second leading cause of end-stage kidney disease in the USA. However, despite its prevalence, the pathologic 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 *(54)*. Loss of renal autoregulation as a result of arterial stiffening, low-grade chronic inflammation, oxidative stress, and altered renin–angiotensin activity are all thought to contribute to renal dysfunction in the context of hypertension *(54)*.

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 *(55)*. More importantly, microalbuminuria is associated with increased risk of cardiovascular as well as all-cause mortality in adult patients with primary hypertension *(56)*. As part of the Bogalusa Heart Study,

Hoq et al. *(57)* 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. In agreement with these findings, Lubrano et al. *(58)* 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) *(58)*. 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 *(58)*.

Studies have also linked the development of changes in renal function to development of cardiovascular complications in hypertensive pediatric patients. Specifically, Assadi *(59)* 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 pediatric nephrology clinic. The results demonstrated a correlation between blood pressure, LVH, and presence of microalbuminuria *(59)*. In regression analysis, CRP, microalbuminuria, and systolic blood pressure were independent predictors of LVH *(59)*. The author speculates that inflammation and microalbuminuria portend increased cardiovascular risk in pediatric patients with hypertension *(59)*. As a result, pharmacologic regimens that target these parameters may improve cardiovascular outcomes in this patient population *(59)*.

The Retina

In a recent study of 800 hypertensive adult patients, the prevalence of early retinal vascular changes was 78% using direct ophthalmoscopy *(60)*. 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 *(61)*. Several population-based studies have also suggested that individuals with retinal microvascular changes have increased cardiovascular morbidity and mortality *(62)*. 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 *(63)*. In a second study of 97 children with essential hypertension, the prevalence of arteriolar narrowing was 41%, tortuosity was 14%, and arteriovenous nicking was 8% *(64)*. In a separate study, Daniels et al. *(65)* examined the predictors of retinal vascular abnormalities in 50 pediatric patients with essential hypertension. In their analysis, diastolic blood pressure and a smaller rise in systolic blood pressure during exercise were independently associated with vascular anomalies *(65)*. 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 *(66)*.

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 *(67)*. Although the etiology of these lesions is unclear, several studies have suggested that elevated blood pressure impairs cognitive functioning in adults *(67)*. Recently, the

Maine–Syracuse Study examined the cognitive functioning of approximately 1500 patients using multiple domains on the Wechsler Adults Intelligence Scale *(68)*. Significant inverse associations between blood pressure parameters and cognitive functioning were observed including measures of psychomotor speed, concept formation, and abstract reasoning abilities *(68)*. Although limited by its cross-sectional design, these results indicated that hypertension is associated with poor performance in several aspects of cognition *(68)*. In agreement with this, Lande et al. *(69)* recently studied the relationship of elevated blood pressure and cognition in school-age children and adolescents. Of the 5077 children studied, 3.4% and 1.6% had systolic and diastolic blood pressures above the 90th percentile, respectively *(69)*. Children with elevated systolic blood pressures but not with diastolic blood pressures demonstrated lower scores on assessments of short-term memory, attention, and concentration *(69)*. Although limited, these data highlight the need for further assessment of cognitive impairment in children with hypertension as well as the need for vigilant screening for hypertension in children to prevent further deterioration of cognitive functioning.

SEQUELAE OF ACUTE HYPERTENSIVE CRISIS

Central Nervous System

Central nervous system abnormalities are typically the most prevalent of end-organ complications in hypertensive crises in children *(70,71)*. Cerebral autoregulation is responsible for maintaining constant cerebral blood flow despite alterations in blood pressure *(72)*. However, as mean arterial pressure increases, disruption of the vascular endothelium and blood–brain barrier leads to fibrinoid deposition within the vascular lumen *(72)*. 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 *(73)*. As an imbalance between oxygen supply and demand develops, cerebral infarction can develop *(73)*. 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% *(74)*. 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 *(75–78)*. Browning et al. *(77)* 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 *(77)*. In contrast, Logan et al. *(78)* reported three cases with permanent reductions in visual acuity despite normal-appearing optic discs. In terms of neurocognitive outcomes, Trompeter et al. *(79)* 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 *(71)*. 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 *(80)*. In an attempt to compensate for increased LV tension, myocytes become hypertrophic *(81)*. In addition, enhanced deposition of extracellular matrix within the ventricle occurs further increasing the oxygen demand of the heart. Continued activation of the

renin–angiotensin axis results in enhanced sodium absorption and increased total body water further worsening ventricular load *(80)*. Because of increased metabolic demands, focal ischemia can develop impairing both left ventricular contraction and relaxation *(81)*. Ultimately, the left ventricle is unable to overcome the abrupt increase in systemic vascular resistance causing left ventricular failure and congestive heart failure *(82)*. 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 *(74)*. It is important to emphasize that clinical findings of congestive heart failure are especially common in neonates with severe hypertension *(83)*.

The Kidneys

Acute renal insufficiency due to altered renal autoregulation and subsequent renal ischemia is also a complication of severe hypertension *(71)*. 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 *(84)*. The presence of thrombosis and microangiopathic hemolysis is thought to portend a poor prognosis *(84)*. In a study of 51 adult patients with malignant hypertension, 46 patients demonstrated renal insufficiency with 67% of patients presenting with a serum creatinine greater than 2.3 mg/dl *(85)*. More importantly, 30% of patients in the study remained on chronic hemodialysis *(85)*. In a study by Gudbrandsson, 50% of patients in hypertensive crisis presented with renal failure *(86)*. 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 *(87–90)*. Development of significant hematuria and proteinuria was also detected in these patients *(87,89)*.

CONCLUSIONS

As illustrated above, significant alterations in end-organ structure and function develop in pediatric patients with hypertension. These data reinforce the importance of prompt recognition and treatment of hypertension in the pediatric population. However, additional studies are required to demonstrate the long-term significance of these alterations and the effect of pharmacologic intervention on altering the progression of end-organ damage in the pediatric population. Improved treatment strategies as well as a better understanding of appropriate blood pressure targets should lead to enhanced long-term outcomes in these patients.

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25 Sleep Apnea and Hypertension

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Contents

INTRODUCTION

Sleep disordered breathing (SDB) encompasses all forms of respiratory disorders specific to sleep *(1)*. There is a spectrum of SDB ranging from mild to severe with the most severe form being obstructive sleep apnea (OSA) *(2)*. In adults, OSA has been linked to cardiovascular disease, specifically hypertension (HTN) *(3)*. The association between systemic HTN and OSA is well documented in both cross-sectional and prospective population studies *(4–6)*. These studies not only demonstrate an association between the two conditions, but one study also documented OSA preceding the development of HTN *(6)*. Additionally, OSA has been associated with drug-resistant HTN in adults *(7,8)* which may be partially mediated by aldosterone *(9,10)*. 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) *(11)*. The National High Blood Pressure Education Working Group for Children and Adolescents made a similar recommendation to evaluate for OSA as a comorbid condition in children with HTN *(12)*. However, the relationship between SDB and HTN is not as clear in children. Regardless, there is evidence to suggest an association between these two conditions, but the causal relationship is still unknown.

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_25
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DEFINITIONS AND EPIDEMIOLOGY OF SDB

OSA in children as defined by the American Thoracic Society is 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 2 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) 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 that 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 CO_2 ($ETCO_2$) and is defined by an $ETCO_2$ > 45 mmHg for more than 60% of total sleep time or any $ETCO_2$ > 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 feature 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)*.

Finally, snoring without obstructive apneas, frequent arousals, or gas exchange abnormalities define 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 between children with primary snoring and those without snoring or SDB. Overall, both groups scored in the average range, but those with primary snoring scored significantly less than the normal controls. This study suggests primary snoring may not be benign and should be considered separately from other forms of SDB and normal controls. Table 1 summarizes the terms and definitions for 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

Table 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

(14,17). In addition, most prevalence studies were based primarily on a variety of questionnaires with few studies performing diagnostic testing for confirmation. Recently, Lumeng and Chervin *(24)* 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. 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, 5.75–9.61). Parent-reported SDB ranged from around 4 to 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 around 1–4%.

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 *(1)*. Arousals may occur frequently without apneic spells manifesting as nighttime restlessness *(25)*. 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 *(20,25)*. Enuresis has also been reported to occur in higher proportions in children with SDB *(26)*. Additionally, studies have shown symptoms of enuresis improve after adenotonsillectomy *(27,28)*. 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-type picture, but they will more likely complain of daytime somnolence and fatigue especially if obesity is also present *(25)*. Obesity is another risk factor for SDB in addition to craniofacial disorders and retro/micrognathia. However, 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 *(1)*. The degree of hypertrophy has been shown to correlate with the duration of obstructive apneas but not with the number of obstructive apneas *(29)*. 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 non-obese children but not for obese children *(30)*. The obese group had a significantly higher Mallampati score than the non-obese 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 (Table 2) on history or physical exam should prompt further evaluation for SDB.

Table 2
Clinical Signs and Symptoms of Sleep Disordered Breathing

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
Adenotonsillary hypertrophy

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 *(25)*. 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 *(31)*. 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)*. 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 is not consistent in the pediatric literature making it difficult to compare multiple studies.

PATHOPHYSIOLOGY

The pathophysiology of SDB in children is complex and not entirely understood, but the two main factors of the upper airway underlying the pathology in children 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 *(32–34)*. On MRI, affected children were also found to have larger adenoids, tonsils, and soft palates *(32)*. Functionally, upper airway patency is maintained during sleep by neuromuscular responses to ventilation, oxygenation, and airway pressure *(17,35)*. On a cross-sectional analysis of children and adults, this response to pressure decreased with age and body mass index (BMI) *(36)*. Additionally, children with OSA were found to have a decreased response to hypercapnia and intermittent acute negative pressure during sleep when compared to controls *(37)*. Not only is the response affected, but Gozal and Burnside *(38)* demonstrated more upper airway collapsibility during wakefulness in children with an AHI ≥ 5. The combination of narrower airways and increased susceptibility to upper airway collapse during sleep are two major contributing factors for the development of SDB in children.

The mechanism underlying the relation between SDB and HTN is complex and multifactorial, and most of the information comes from adult data. The autonomic nervous system plays a major role, but other factors have been identified including vasoactive substances, endothelial dysfunction, and intrathoracic changes. Normally, heart rate, BP, and sympathetic activity decline during sleep, but intermittent hypoxemia, hypercapnia, and arousals activate the sympathetic nervous system *(39,40)*. These surges in sympathetic activity during sleep result in increased BP and heart rate that can persist into wakefulness *(41)*. The vasoactive substances found to correlate with OSA in adults include endothelin *(42)* and aldosterone, but increased aldosterone has been limited to adults with resistant HTN *(9,10)*. Other vasoactive substances 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 *(43)*. There is evidence of endothelial dysfunction in children with OSA that improved after adenotonsillectomy *(38)*. Finally, changes in intrathoracic pressure may contribute to the autonomic responses during sleep in patients with OSA leading to activation of the sympathetic nervous system and ultimately raising BP *(40)*. In addition to raising BP, intrathoracic pressure may also have an effect on 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 ele-

vated left ventricular transmembrane pressures were detected during the ventilatory period following an obstructive apnea in adults with congestive heart failure *(44)*. This increase in cardiac afterload following obstructive apneas may explain the presence of left ventricular hypertrophy (LVH) in patients with OSA independent of BP *(45)*.

SDB AND HYPERTENSION

Similar to the epidemiologic studies of SDB in children, studies evaluating the association of BP with SDB are heterogeneous and differ by the methods and criteria used to diagnose SDB and to measure BP. Some studies measured casual BP either with oscillometric devices *(46,47)*, calibrated sphygmomanometers *(48)*, or mercury manometers *(49)*. The remaining studies measured ambulatory blood pressure (ABP) during wake and sleep *(50–53)* or only in relation to the PSG *(54,55)*. Most of the studies analyzed raw BP values, but some studies indexed BP to the 95th percentile according to various reference values in order to assess HTN status. In regards to SDB, participants were divided into two or three groups depending on AHI or snoring. Among the studies analyzing the association between BP and SDB (Table 3), there is no clear consensus on how the two conditions relate. One of the earliest reports in children was a case series by Guilleminault et al. *(56)* where five of the eight children with sleep apnea had HTN. A later study assessing BP during PSG found significantly higher wake and sleep diastolic BP in children with OSA than those with primary snoring *(55)*. 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.

Subsequent studies reported similar findings but also detected a difference in systolic BP *(48,52,54)*. One study divided the participants into high AHI (AHI $\geq$ 10) and low AHI (AHI < 10) groups and used a BP index defined as the difference between mean BP and cutoff values for age *(54)*. 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 defined three SDB groups by AHI but excluded primary snorers (AHI < 1 and snoring > 3 times per week): (1) AHI < 1, (2) AHI between 1 and 5, and (3) AHI > 5 *(52)*. Mean BP was converted to a z-score according to the LMS method described by Wuhl et al. *(57)* 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 that was no longer significant after controlling for BMI. A different study evaluating BP as a component of the metabolic syndrome in adolescents also demonstrated patients with SDB (AHI $\geq$ 5) had significantly higher systolic and diastolic BP even after adjusting for age and BMI percentile *(48)*.

Other studies were less consistent with the differences in diastolic BP *(46,50,51,53)*. Leung et al. *(53)* compared a high AHI (AHI $\geq$ 5) and a low AHI (AHI < 5) group by 24-h ABP variables with a BP index defined as the measured BP divided by the 95th percentile for ABP *(53)*. 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 study population to complete PSG did not find a difference in diastolic BP among the three SDB groups: (1) no SDB, AHI < 1; (2) mild SDB, AHI 1 to < 5; and (3) moderate SDB, AHI $\geq$ 5) *(46)*. 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.,

Table 3
Comparison of Blood Pressure Studies and Sleep Disordered Breathing in Children

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. *(56)*	Case series of patients with OSA	NR	Presence or absence of HTN	NR	NR	NR	N/A
Marcus et al. *(55)*	OSA vs primary snoring	Oscillometric during PSG	BP index	No difference	Elevated wake and sleep	NR	No difference
Kohyama et al. *(54)*	Low vs high AHI	Oscillometric during PSG	BP index	Elevated wake and REMS	Elevated wake and REMS	NR	No difference
Li et al. *(52)*	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. *(48)*	SDB vs no SDB	Aneroid manometer	Raw values	Elevated	Elevated	NR	N/A
Leung et al. *(53)*	Low vs high AHI	ABPM	BP index	Elevated wake and sleep	Elevated sleep	NR	No difference
Bixler et al. *(46)*	Controls, mild, moderate SDB by AHI	Oscillometric	Raw values	Elevated	No difference	Elevated	N/A
Kaditis et al. *(47)*	Snorers vs non-snorers by questionnaire	Oscillometric	Raw values	No difference	No difference	NR	N/A
Amin et al. *(50)*	Controls, mild, moderate SDB by AHI	ABPM	BP index and BP variability	No difference	Lower during wake	No difference	Linear trend across SDB groups

Table 3
(continued)

Source	*SDB classification*	*Method of BP measurement*	*Method of BP analysis*	*Systolic BP results*	*Diastolic BP results*	*Mean arterial BP results*	*Nocturnal dip*
Amin et al. *(51)*	Controls, mild, moderate SDB by AHI	ABPM	Raw values	Elevated wake	Elevated wake and sleep	Elevated wake and sleep	NR
Enright et al. *(49)*	RDI	Mercury manometer	HTN vs normal	HTN associated with RDI	HTN associated with RDI	NR	N/A
Reade et al. *(65)*	OSA vs non-OSA	Manual BP	BP score	Elevated	Elevated	NR	N/A

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 monitor; RDI, respirator disturbance index.

AHI ≥ 1, AHI ≥ 2, etc.), 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.

Only one study failed to detect any difference in BP between SDB groups, but these groups were defined by questionnaire alone into habitual and non-habitual snorers *(47)*. One study actually detected a lower diastolic BP in the group with the highest AHI *(50)*. This study defined three groups by AHI: (1) primary snorers, no evidence of nocturnal hypoventilation and an AHI <1; (2) Group 2, AHI from 1 to 5; and (3) Group 3, AHI > 5. For this study, 24-h ABP was measured and BP index ((measured BP – 95th percentile)/95th percentile × 100) was compared across the three groups. The authors also analyzed BP variability defined as the average standard deviation of awake and sleep systolic, diastolic, and mean arterial BP. 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 level in Group 3. On the contrary, there was a dose-dependent increase in wake systolic BP variability across the three groups. A similar trend was demonstrated for wake mean arterial BP and for all sleep BP. The authors propose the variability in BP during both sleep and wakefulness suggests autonomic instability in children with SDB resulting in BP dysregulation. The same group later performed a separate but similar, more rigorous study and did detect significantly elevated BPs (except for sleep systolic BP) in those with an AHI > 5 compared to controls with an AHI <1 *(51)*. 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 this 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 *(59–61)*. 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. This was the first study evaluating the association of the morning surge with SDB in children, and its implication in children is currently unknown. Although echocardiographic measures of the left ventricle were assessed in this study, there was no report of their relationship to the morning surge.

Despite significant BP differences among a variety of SDB groups, none of the groups had mean BPs consistent with HTN defined by a BP ≥ 95th percentile according to reference values for casual measurement *(12)* or for ambulatory measurements *(57,62)*. Enright et al. *(49)* evaluated BP in terms of HTN and dichotomized BP into HTN or normal *(49)*. 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 *(58)*. One of the previously mentioned studies by Leung et al. *(53)* also estimated HTN prevalence defined as a mean wake, sleep, and/or total ABP ≥ 95th percentile for ABP reference values *(62)*. 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 not a significant predictor of HTN except among those with obesity.

Obesity must be considered when analyzing the relationship between SDB and HTN since obesity is associated with both conditions *(63,64)*. In the previous study by Li et al. *(52)*, BMI was found to be a confounding factor for wake systolic BP, that is, the association was no longer significant when controlled for BMI. 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 *(46,49–55)*. In one of the studies, SDB

remained a significant predictor of BP when controlled for BMI, but the effect of BMI on BP was not reported *(48)*. There was one study, not yet mentioned, specifically designed to address the interaction between SDB, BP, and obesity *(65)*. The specific aim 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 by 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 *(58)*, 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 non-obese, 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 for the OSA and the obese groups. For obese hypertensives, only BMI was significant for systolic BP score. The interaction between OSA, HTN, and obesity is significant, and 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

BP has a normal physiologic decline during sleep commonly referred to as the nocturnal dip *(66)*. The normal mean nocturnal dip is typically 10–20% less than the mean daytime BP *(67)*. Abnormal nocturnal BP patterns can vary from a minimal decline in nocturnal BP (<10% dip) to a rise in nocturnal BP above normal daytime values *(68)*. The prevalence of nondipping in adults with OSA is 48–84% *(8,69,70)*. When compared to controls in one study, only patients with OSA were nondippers 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 nondipping status *(70)*. In children, the relationship between nocturnal dipping status and SDB has not been consistent *(50,52–55)*. From the previously mentioned studies evaluating BP during sleep and wake, most do not show a statistically significant difference in the proportion of nondippers among children with SDB compared to those without SDB *(52–55)*. Two of the studies demonstrated a higher proportion of nondippers 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 *(54,55)*. Rather than comparing the proportion of nondippers, two studies examined the mean nocturnal dip per group defined by AHI (AHI < 1, AHI 1–5, and AHI > 5) *(50,52)*. In the first study, the average nocturnal dip per group significantly decreased for systolic, diastolic, and mean arterial BP across the three groups *(50)*. The proportion of nondippers 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 nondippers per group *(52)*. 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

LVH is the most commonly recognized surrogate marker of end-organ damage in children and adolescents with systemic HTN *(12)*. In adults with OSA, the intermittent obstructive apneas lead to an increase in afterload *(44)* possibly contributing to the development of LVH. Therefore, patients with both HTN and OSA may have an even greater risk of LVH. Adult data suggest that LVH is independently associated with OSA *(45,71)*. 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 *(72)*. Furthermore, on stepwise multiple regression analysis, AHI was the only significant predictor of LVMI even when age, gender, and BMI were forced into the model. Participants with an AHI > 10 were about 11 times more likely to have LVH independent of age, gender, and BMI. Resting BP was not a significant predictor and, therefore, not included in the final model. This dose-dependent effect of the severity of SDB on LVMI was consistent in a later report from the same group with additional participants *(73)*. 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: (1) controls, AHI < 1 and no history of obstructive breathing during sleep; (2) moderate, AHI 1 to < 5; (3) severe, AHI ≥ 5 *(51)*. They found a progressive, but insignificant, increase in LVMI across the three groups with worsening AHI. 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 *(74)*. Although evidence suggests 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 generally the first-line treatment for OSA in children *(22)*. 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)*. CPAP is fairly well tolerated in children, but for effectiveness, compliance is crucial and can be poor secondary to minor side effects such as rhinorrhea, nasal congestion, or dryness *(1)*. Studies have demonstrated significant improvement in the AHI and in behavioral and cognitive symptoms after treatment of SDB *(75,76)*, and some studies have even shown an improvement in left ventricular geometry and/or function *(73,77)*. For example, one of the previously mentioned studies by Amin et al. *(73)* compared pretreatment and posttreatment left ventricular diastolic function by mitral inflow velocity. 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 *(77)*. Few studies have reported the treatment effect of SDB on BP in children. In the aforementioned case series by Guilleminault et al. *(56)* five of the eight patients with OSA had HTN at presentation. Those who underwent adenotonsillectomy and demonstrated improvement of symptoms on follow-up PSG were no longer hypertensive on follow-up. 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. One study specifically evaluated the effect of adenotonsillectomy on BP in children *(78)*. Children with complete resolution of SDB after surgery (AHI < 1) had a significant decrease in diastolic BP but not in systolic BP. Although the association between drug-resistant HTN and OSA has been described in adults *(7,8)*, there are currently no reports in children. However, in a child with risk factors for SDB and difficult to control HTN the presence of SDB should be considered.

CONCLUSION

Despite the heterogeneity, the studies in children and adolescents suggest that a relationship exists between elevated BP/BP variability and SDB. This relationship is significant independent of obesity, but obesity also has an independent association with SDB and with HTN *(63,64)*. How the three conditions interact and whether there is a causal relationship among the conditions is unknown and requires further investigation. In adults, both HTN and SDB are independently associated with significant cardiovascular events. Fortunately, the same cardiovascular events do not occur in children, but the changes in left ventricular structure and function have been shown to occur. 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 if obesity is also present.

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26 Hypertension and Exercise

Rae-Ellen W. Kavey, MD, MPH

CONTENTS

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. 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 it increases in both sexes with increasing age and body size *(2)*. Both lean body mass and fat mass are important hemodynamic determinants of blood pressure *(6)*. Consistent racial differences in the BP response to 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 BPs, a modest increase in heart rate, stable or limited decline in stroke volume, a small increase in cardiac output, and no change in systemic vascular resistance *(4,8–10)*. The increase in systolic and diastolic BPs can be marked. In young adult male weight lifters, extremely high blood pressures, exceeding 400/300 mmHg, have been reported from direct intra-arterial recordings *(11)*.

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_26
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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 *(2–5,7,13–26)*, with exercise blood pressures monitored manually or with automated instruments *(12,27)*. The use of varying protocols makes direct comparison of these results difficult.

There is agreement that 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 blood 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 has been defined as 220 mmHg. However, measurement of BP response with radial artery catheterization in adults during exercise testing reveals 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 nonhypertensive 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". Other expert commentaries have also recommended routine dynamic exercise and no exercise limitation in hypertensive children and adolescents on therapy *(30,37–39)*.

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 *(40–42)*. In children, the

predictive value of exercise BP has been 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 *(43)*. In normotensive adolescents, systolic BP response to exercise was significantly higher in those with a family history of hypertension than in controls with a negative family history *(44)*. In 7- to 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 bicycle ergometer testing *(45)*. In a larger group from the same laboratory, 1-year stability was demonstrated for dynamic pressor responses in children from hypertensive families *(46)*. Evaluation of the pressor response to treadmill exercise in 6- to 7-year-old black and white children showed that stress responses are predictive of resting cardiovascular function at 2.5 year follow-up *(47)*. 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. By contrast with other reports, the 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 but no increase in blood pressure *(48)*. In a small series of boys with severe hypercholesterolemia, exercise systolic and diastolic blood pressures were found to be significantly higher than those of normolipidemic controls, suggesting altered control of arterial vascular tone in this setting *(49)*. 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 summary, the BP response to exercise appears to be exaggerated in children who are at increased risk for 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 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 *(50–52)*. 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 *(53–56)*. This has been attributed to a variety of mechanisms, including histologic and physiologic abnormalities of the aortic wall *(57)*, altered baroreceptor function *(58)*, increased vascular resistance and abnormal vasodilator function in the upper body *(59)*, increased norepinephrine response to exercise with increased plasma renin levels *(60)*, altered flow around the surgically altered aortic arch *(61)*, and altered mechanics at the repair site *(62,63)*. The significance of isolated exercise hypertension in postcoarctectomy patients and its relation to clinical outcome is not known and some have suggested that exercise testing results in this context are not meaningful *(64)*. However, exercise-induced hypertension 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 *(65)*. 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 postcoarctectomy patients who warrant antihypertensive treatment. Cardioselective beta-blockade has been shown to be effective in this setting *(66)*.

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 *(67,68)*. With exercise testing, this is associated with a blunted blood pressure rise, the development of anginal or presyncopal 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 *(69)*. 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 months) follow-up *(70–73)*. 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 *(74)*. 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 *(75)*.

In children with aortic valve stenosis, results have been less consistent. Beginning in the 1960s, characteristic ischemic ECG changes of ST segment depression with exercise have been reported in children with aortic valve stenosis; the presence and severity of the ischemic response correlated with the magnitude of the aortic valve gradient *(76–78)*. 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 *(79–81)*. 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 *(82)*. 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 conception of myocardial ischemia as the etiology of ischemic electrocardiographic findings *(83)*. 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 *(84,85)*. 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 as part of the routine evaluation and follow-up of children with moderate and severe aortic stenosis *(86)*. 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 *(87)*.

Hypertrophic Cardiomyopathy

Sudden death is a dreaded and relatively common occurrence in patients with hypertrophic cardiomyopathy (HCM)and the risk of sudden death is greatest in children and young adults *(88–90)*. 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 *(91)*. Invasive studies have shown that the failure to increase blood pressure appropriately during exercise is a consequence of an inappropriate vasodilator response in non-exercising vascular beds leading to an exaggerated fall in systemic vascular resistance, impaired diastolic filling capacity, and a blunted increase in stroke volume *(92,93)*. Left ventricular outflow tract gradient has been shown to increase markedly when measured immediately after exercise; independent predictors of an increase in outflow gradient with exercise included a history of syncope or presyncope *(94,95)*. An abnormal exercise blood pressure response has also been related to subendocardial ischemia in patients with HCM *(96)*. Finally, a recent study using ambulatory radionuclide monitoring demonstrated that an abnormal blood pressure response was associated with exercise-induced left ventricular systolic dysfunction and impairment in oxygen consumption *(97)*. 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 subsequent follow-up, an abnormal BP response to exercise was shown to be associated with increased risk of sudden cardiac death with high-negative but low-positive predictive accuracy *(98–100)*. In addition to the abnormal hemodynamic response, exercise testing and ambulatory ECG monitoring demonstrate a high prevalence of atrial and ventricular arrhythmias *(101)*.

While most of the studies reported above have included children and adolescents, there have been some that have 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 *(102)*. 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 *(103)*. 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 *(104)*. All patients survived testing but 19% developed chest pain with significant ST depression and 42% had a hypotensive response to exercise. Mean exercise duration was reduced for the group. Unfortunately, exercise results were only available for 1 of the subset of 12 patients from the whole group who went on to sudden death; in that child, there was a BP drop with exercise. Finally, a consecutive series of children with HCM were evaluated by echocardiography, ambulatory ECG monitoring, and exercise testing *(105)*. 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 analysis, 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.

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 *(106)*. However, 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.

EXERCISE AS NONPHARMACOLOGIC TREATMENT OF ESSENTIAL HYPERTENSION

When essential 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 book, the BP-lowering effects of weight loss and diet change are presented. Here, the BP-lowering effect of exercise is reviewed.

Many epidemiologic studies 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- to 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, there was a decrease of 1.15 mmHg in systolic BP *(107)*. 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 *(108)*. In the Northern Ireland Young Hearts project, a random cohort of 12- to 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 *(109)*. Finally, in the Young-HUNT study from Norway, activity levels, weight measures, and BPs were evaluated in more than 8000 adolescents. In this population, low levels of physical activity were significantly associated with higher mean diastolic BP and increased odds of overweight and obesity *(110)*.

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 *(111)*. The review included 12 trials representing 16 outcomes in 1266 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. Two subsequent trials confirm significant blood pressure-lowering effects of exercise in children *(112,113)*. 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 longitudinal studies and the intervention studies 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 essential 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 Committee on Sports Medicine and Fitness recommends restriction from weight- and powerlifting, body building, and strength training in children with hypertension; participation in competitive sports is given a "qualified yes" *(114)*. In previous guidelines from the AAP that focused specifically on children with hypertension, children with severe hypertension are limited from competitive sports until BP is adequately controlled *(115)*. Many other expert commentaries have also recommended regular dynamic exercise and no exercise limitation in hypertensive children and adolescents on effective therapy *(30,37–39)*.

Overall, the consensus appears to be no dynamic exercise limitations in children and adolescents once BP has been treated. There are some reservations about static exercise in hypertensive patients. However, beyond the potential for extreme pressure elevation with resistance training that has been documented in normotensive subjects, the basis for this is limited, especially in light of studies documenting a fall in blood pressure with a sustained resistance training program *(11,111)*.

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27 Hypertension in the Developing World

Vera H. Koch, MD

Contents

THE EPIDEMIOLOGICAL TRANSITION OF THE DEVELOPING WORLD

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 associated with increased wealth providing the opportunity to spend extra resources on poor health habits such as 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 life spans.

The present picture of health problems around the world, however, now reflects a different reality. In 2002, the two most common causes of death in the world were ischemic heart disease (accounting for more than 7 million deaths) and cerebrovascular disease (approximately 5.5 million deaths) *(1)*; these comprised 12.6 and 9.6%, respectively, of all deaths worldwide *(2)*. One may presume that the majority of these deaths occurred in developed countries, but when countries are grouped according to their state of economic and demographic development and their mortality patterns, it is possible to realize that the number of deaths from cerebrovascular disease in developed countries comprised less than one-third of deaths from this disease worldwide. Similar distribution patterns

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_27
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emerge for ischemic heart disease *(3)*. Thus, despite the fact that the burden of disease in developed countries still largely reflects the problems associated with wealth, there is an enormous burden of chronic non-communicable diseases among populations in developing countries *(4)*.

The emergence of chronic diseases in developing countries is thought to be due to changes in the demographic structure of the population, as well as to epidemiological transitions *(1)*. These changes have traditionally occurred with economic development, have evolved over hundreds to thousands of years, and have involved an evolution from times of high mortality and low population growth to periods of increased life spans and receding pandemics. The final progression is then on to degenerative and man-made diseases, such as cardiovascular disease, 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)*. Presently, although developing countries are experiencing a decline in the prevalence of infectious diseases, this is far outweighed high rates of both infectious and chronic diseases.

The risk factors underlying the emergence of non-communicable disease in these developing countries follow the same patterns as those identified previously in the current established market economies. These include increased levels of alcohol consumption, tobacco smoking, obesity, physical inactivity, and low fruit and vegetable intake. In parallel with this, there is also increased evidence of high cholesterol levels and, in particular, high blood pressure *(6)*.

The emergence of the cardiovascular disease (CVD) epidemic in the 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 *(7)*, conducted in search of published studies, which reported the prevalence of hypertension in representative population samples, 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. The authors 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.

The present high burden of CVD deaths is in itself an adequate reason for attention; however, another important cause for concern is the early age of CVD deaths in the developing countries compared with the developed countries. In 1990, the proportion of CVD deaths occurring below the age of 70 years was 26.5% in the developed countries compared with 46.7% in the developing countries *(8)*. The contrast between the truly developed countries (22.8% of CVD deaths at <70 years) and a large developing country like India (52.2%) was even sharper *(8)*. Therefore, the contribution of the developing countries to the global burden of CVD, in terms of disability adjusted years of life lost, was 2.8 times higher than that of the developed countries.

As a consequence of the epidemiological transition, life expectancy in developing countries has risen, due to a decline in deaths occurring in infancy, childhood, and adolescence, and was related to more effective 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. The increasing longevity provides longer periods of exposure to the risk factors of CVD *(9)*, resulting in a greater probability of clinically manifest CVD events *(10)* and leading to a projected rise in both proportional and absolute CVD mortality rates in the developing countries *(1)*. Hypertension is projected to be one of the major risk factors underlying the global burden of disease in 2020 *(4)*.

THE FETAL ORIGINS HYPOTHESIS AND DOHAD—DEVELOPMENTAL ORIGIN OF HEALTH AND ADULT DISEASE

The "early" or "fetal" origins of adult disease hypothesis was originally put forward and further developed by David Barker and colleagues in Southampton in the United Kingdom which stated that environmental factors, particularly nutrition, act in early life to program the risks for the early onset of cardiovascular and metabolic disease in adult life and premature death *(11–22)*. 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 *(23–25)*. In 1992, Hales and Barker *(26)* coined the term the "thrifty phenotype" hypothesis, derived from the prior "thrifty genotype" hypothesis *(27)* 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. 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 *(26,28)*. This concept is consistent with the definition of "programming" by Lucas in 1991 *(29)* 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 *(30,31)*. 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; each stage can be affected by programming mechanisms of adult disease *(32–34)*. As in other species, developmental plasticity attempts to "tune" gene expression to produce a phenotype best suited to the predicted later environment *(35)*. 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 risk of disease increases. Thus, the degree of the mismatch determines the individual's susceptibility to chronic disease *(36)*.

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 *(36,37)*, 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 created by Waddington *(38)* to refer 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 *(39)*.

The degree of mismatch can by definition be increased by either poorer environmental conditions during development or richer conditions later or both *(36)*. Such changes are of considerable importance in developing societies going through rapid socioeconomic transitions and represents 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 *(40)*. Attention continues to focus primarily on fetal growth. Impaired growth during this critical period of organ development may have an impact on disease risk by permanently reducing the number of functional units, including nephrons *(41)*. 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 glucocorticoid hormones, ligation of the uterine artery, experimentally produced anemia, and alteration of postnatal growth *(32)*. 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 *(32)*.

Several animal studies were devised to evaluate the effect of perinatal interventions on renal organogenesis and postnatal renal function. Table 1 depicts some of these studies and the main results in the offspring.

Table 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. *(42)*	Late gestational exposition to gentamycin	• Oligonephronia • Early nephron compensatory adaptation • Progressive glomerular sclerosis
Celsi et al. *(43)*	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. *(44)*	Gestational exposition to mild vitamin A deficiency	• Oligonephronia
Vehaskari et al. *(45)*	Gestational exposition to low-protein diets	• Oligonephronia • Apoptosis • ⇓ PRA • ⇑ Aldosterone • Arterial hypertension
Woods et al. *(46)*	Gestational exposition to low-protein diets	• Oligonephronia • Glomerular enlargement • ⇓ Renal renin mRNA • Arterial hypertension
Pham et al. *(47)*	Uteroplacental insufficiency	• Oligonephronia • Apoptosis • Arterial hypertension

Evidence of Epigenetic Mechanisms in Animals and Its Importance as a Cause of Adult Nephropathy and Arterial Hypertension

Human studies have provided evidence suggesting nongenomic inheritance across generations. Patterns of smoking, diet, and exercise can affect risk across more than one generation *(48)*. 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 *(49)*. Famine exposure at different stages of gestation was variously associated with an increased risk of obesity, coronary heart disease, elevated albuminuria, later insulin resistance, and

Table 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. *(64)*	South Africa	5-year-old children	Inverse relation between BW and SBP	–
Law et al. *(65)*	China, Guatemala, Chile, Sweden	3- to 6-year-old children Term pregnancy BW > 2.5 kg	Inverse relation between BW and BP	Current WT
Bavdekar et al. *(66)*	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
Walker et al. *(67)*	Jamaica	11- to 12-year-old children	Inverse relation between SBP and BW	Postnatal growth retardation Current WT
Barros and Victora *(68)*	Brazil	14- to 15-year-olds	No association between BW and BP	Arterial hypertension More frequently diagnosed in adolescents born SGA
Adair and Cole *(69)*	Philippines	14- to 16-year-olds	Higher prevalence of elevated BP in low BW males	Weight gain from late childhood into adolescence in males with low BW
Nelson et al. *(70)*	PIMA Indians (USA)	Adults Type 2 diabetes	Association of ↑ albuminuria with BW <2.5 kg BW >4.5 kg	
Hoy et al. *(71)*	Australian Aborigines	Adults	Inverse relation between BW and albuminuria	

BP, blood pressure; SBP, systolic blood pressure; BW, birth weight.

dyslipidemia *(50)*. 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 *(49)*.

Barker and colleagues' observations 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 *(11–22)*. These observations have been corroborated and extended by other epidemiologic studies and studies in twins *(50–61)*.

The interest in this field has grown rapidly over the past decade. However, the most critical questions in this field remain unanswered. First, which of the children who have biochemical markers of metabolic disease will go on and develop overt metabolic disease in adult life? Second, what are the initiating events that trigger persistent metabolic programming? Third, what are the mechanisms that lead to adverse programmed metabolic changes *(62)*? 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 >2500 g *(63)*.

A list of selected epidemiological studies investigating the association of birth weight with different clinical outcomes along the human life cycle in developing countries and underprivileged populations is shown in Table 2.

THE FUTURE OF CARDIOVASCULAR DISEASE IN THE DEVELOPING WORLD

As we have discussed there is a high burden of CVD morbidity and mortality in the developing countries, affecting individuals at a younger age than observed in developed countries *(8)*. 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 of CVD, resulting in a greater probability of clinically manifest CVD events *(10)*.

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 *(72)*, 30 million low birth weight babies are born annually (23.8% of all births). Although the global prevalence of such births is slowly dropping, 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. Besides its negative impact on birth weight and early development, low birth weight results in substantial costs to the health sector and imposes a significant burden on society as a whole. Table 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. The high prevalence of short stature in children of developing countries is depicted in Fig. 1, showing high rates in important areas of the world, including India.

An enormous task awaits developing countries, as national strategies to control the CVD epidemic must be developed and effectively implemented by individual countries. In par-

Table 3
Percentage and Number of Low Birth Weight Infants (LBW) According to the World Region and World Health Organization Region Development Classification, 2000

	% LBW	*No LBW/1000*	*No live births/1000*
World	15.5	20,629	132,882
Developed	7.0	916	13,100
Less developed	16.5	19,713	119,721
África	14.3	4320	30,305
Ásia	18.3	14,195	77,490
Europe	6.4	460	7185
Latin America and Caribbean	10.0	1171	11,671
North America	7.7	348	4479
Oceania	10.5	27	255

Modified from *(73)*.

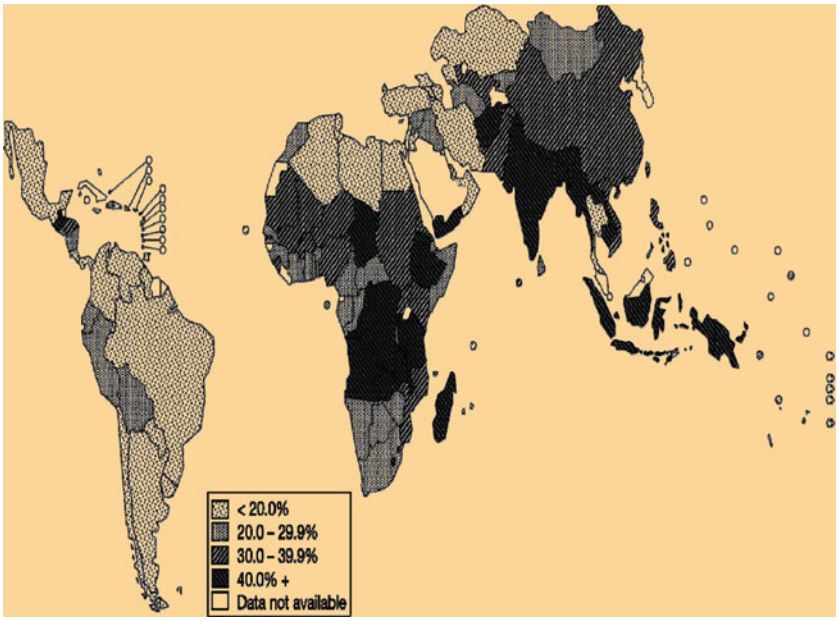

Fig. 1. Prevalence of short stature in children younger than 5 years of age in developing countries (from *(74)*).

allel, individual national efforts could be definitely strengthened by regional and global initiatives by international agencies concerned with health-care program facilitation, policy development and research funding. 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" *(75)* and the "Making pregnancy safer" program *(76)*, 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 breast-feeding during at least the first 6 months to ensure child health and survival. Breast-feeding is also important for provision of sufficient caloric intake for growth, without incurring in the dangers of overfeeding and higher weight gain in early childhood, which are associated with the use of nutrient-enriched formula, and may predispose to hypertension and metabolic syndrome in later life *(77,78)*.

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 *(79)*. These principles should be also ensured for the general population with age and gender adaptations.

Other essential components of a CVD control program would be the following: (1) establishment of efficient systems for estimation of CVD-related burden of disease and its secular trends; (2) estimation of the levels of established CVD risk factors (e.g., smoking, elevated cholesterol, or blood pressure) in representative population samples to help identify risk factors that require immediate intervention; (3) evaluation of emerging risk factors (e.g., glucose, abdominal obesity, fibrinolytic status, homocysteine) that may be of special relevance to the populations concerned; (4) identification of the determinants of health behavior that influence the levels of both traditional and emerging risk factors in the specific context of each society; and (5) development of a health policy that will integrate population-based measures for CVD risk modification and cost-effective case management strategies for individuals who have clinically manifested CVD or are detected to be at a high risk of developing it.

All of these require a strengthening of policy-relevant research that can support and evaluate CVD control programs in the developing countries. The challenge of CVD control is especially complex in settings in which epidemiological data related to the incidence of fatal and nonfatal CVD events as well as population-attributable risk of various risk factors of CVD are not readily or reliably available at present *(80)*.

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IV Evaluation and Management of Pediatric Hypertension

28 Evaluation of the Hypertensive Pediatric Patient

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Contents

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 must be given to the causative spectrum of hypertension in pediatric patients as it is broad and changes with age. Most infants, toddlers, and school-aged children must be presumed to have secondary hypertension, with primary hypertension most prevalent in adolescence. For children with severe hypertension, those above the 99th percentile, careful, comprehensive, and immediate evaluation is required. A rule of thumb for the identification of children with secondary hypertension is when the hypertension is severe and the child is young, with the highest sensitivity found in the youngest and most severely hypertensive. However, this may not always be the case, and therefore evaluation is important as the cause may be remediable and benefit from 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 *(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)*.

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_28
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Unlike in adults, the diagnosis of pediatric hypertension predominantly is founded on epidemiologic and expert opinion data rather than being driven by evidence-based outcomes *(2)*. Recently, however, a 5-year randomized trial has been published showing the benefit of renoprotective therapy on retarding the progression of renal disease in children *(4)*; hopefully, this will lead to development of evidence-based treatment recommendations. The necessity for further 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 and 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; those that have been can be found at the web site www.dableducation.org. Studies that compare oscillometric devices to auscultatory sphygmomanometry show poor correlation, highlighting the need for confirmation by auscultatory methods. As BP is a continuous variable, assuming a single clinic BP (CBP) measurement representative of the patient's true BP pattern may not be reasonable; ambulatory BP monitoring (ABPM), on the other hand, is considered to be superior to CBP for the prediction of cardiovascular events. With this in mind, ABPM is now increasingly recognized as being indispensable for the diagnosis and management of hypertension *(8–11)*. 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 *(10)*. 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 *(12,13)*. McNiece et al. in 2007 linked the severity of hypertension to the odds of having left ventricular hypertrophy *(14)*. Others have shown thicker carotid arteries with higher ABPM levels *(15,16)*.

The use of home BP measurement in children and adolescents has limited evidence, but can be a technique for BP monitoring, suggest the diagnosis of white coat hypertension (WCH), and monitor antihypertensive therapy. Wuhl 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 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 *(17)*. 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 advantages include lower cost and user acceptance *(18)*.

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 *(19)*. Approximately 60% of overweight (BMI > 95th percentile) youths have at least one risk factor for future cardiovascular disease, including elevation of BP, abnormal lipids, and insulin resistance *(20)*. ABPM may facilitate the differentiation of

Table 1
Phases of Hypertension Evaluation

Phase 1: Is the Patient Truly Hypertensive in the Non-medical Setting?
Ambulatory blood pressure monitoring
Self-measured blood pressure
School-based blood pressure measurements
Phase 2: Screening
CBC
Urinalysis
Urine culture
Serum chemistries
Electrolytes (potassium, sodium, chloride, bicarbonate, glucose)
Creatinine, BUN
Lipoprotein profiling (serum total cholesterol, with high-density lipoprotein, low-density lipoprotein, and triglycerides)
Renal ultrasound with Doppler
Echocardiogram/EKG
Phase 3: Definition of Abnormalities
Renal imaging
• Renal ultrasound with Doppler plus/minus radionuclide scan
• VCUG
Renovascular imaging (noninvasive), CT or MRI angiography
Captopril challenge
Renin profiling
Aldosterone, catecholamine profiling
Abdominal imaging; CT or ultrasound
Phase 3a: Identification of End-Organ Damage
Echocardiography
Retinal examination
Urine protein quantification
Phase 4: Determination of Significance and Remediability of Abnormalities
Arteriography (conventional or digital subtraction angiography)
Renal vein renin collection
Renal biopsy
MIBG scans (pheochromocytoma)

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 *(21)*.

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 1 and 2). We use the term 'phase' of evaluation in an attempt to lessen confusion with 'stages' of hypertension used in Table 3.

Phase 1: Is the Patient Truly Hypertensive in the Non-medical 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)

Table 2
Questions to be Addressed in Phase 2 Evaluation After the Hypertension Has Been Confirmed

Test	*Design*
What has hypertension done to the patient?	
Examination of history	
Measurement of growth	
Urinalysis	Renal disease (microalbuminuria, proteinuria, hematuria)
Echocardiogram	Left ventricular hypertrophy
Poor growth	Chronic kidney disease
Fundoscopic examination	Chronic hypertension
Hemoglobin/hematocrit	Renal dysfunction/anemia of CRF
Serum electrolytes, Ca, and phosphate	Renal dysfunction
What other risk factors for cardiovascular/kidney disease are present?	
Fasting blood sugar	Diabetes
Elevated HgA1c	Diabetes
Glucosuria	Diabetes
Weight	Obesity
Lipoprotein analysis	Hypercholesterolemia; hypertriglyceridemia
Family history	Cardiovascular, obesity
Personal history	Medications, smoking, inactivity
Why does the patient have hypertension?	
Serum electrolytes	1° or 2° aldosteronism
BUN and S_{cr}	Renal dysfunction
Uric acid	Primary HTN marker (?)
Renal ultrasound	Anatomic or pathologic etiology
Urinalysis	Hematuria/proteinuria (nephritis, renal masses)
Weight	Obesity

Table 3
Classification of Hypertension in Children and Adolescents

Normal blood pressure	*SBP and DBP <90th percentile*
Prehypertension	SBP or DBP ≥90th percentile but <95th percentile
Hypertension	SBP or DBP ≥95th percentile
Stage 1 hypertension	SBP or DBP from 95th percentile to 99th percentile plus 5 mmHg
Stage 2 hypertension	SBP or DBP >99th percentile plus 5 mmHg

SBP = systolic blood pressure; DBP = diastolic blood pressure.
Percentiles are for sex, age, and height for blood pressure measured on at least three separate occasions.
Characterized by higher percentile if SBP or DBP percentiles are different.
Adapted from *(2)*.

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 Non-medical Setting?

When a child is found to have an elevated BP this should elicit, *before* a thorough evaluation is performed, further validation 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 Fourth Report nomograms at each measurement session *(2)*. Accurate measurement of BP is dependent on a number of factors including use of the appropriate sized cuff. For 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. If a BP cuff is used with an inappropriate small cuff, BP may be falsely overestimated.

Confirmation of BP elevation should be repeated on at least three separate occasions unless it is severe (greater than or equal to stage 2 hypertension) or the child is symptomatic. In the latter case, one should make immediate referral to a specialist in pediatric hypertension or admission to a hospital or emergency room. 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. However, school BP equipment may not be regularly calibrated and the training of school nurses may vary widely; therefore, proper training of the nurses and validation of equipment used at local schools is time well spent. Ideally ABPM should be used to confirm the diagnosis of hypertension and to exclude the diagnosis of WCH *(22)*. One must also note that a small percentage of patients similar to those reported by Lurbe and colleagues *(23)* who have normal casual BP measurements have elevated ambulatory BP measurement, i.e., masked hypertension. With regard 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 true hypertension *(24)*. An algorithm for the evaluation of hypertension using different BP measurement techniques can be found in Fig. 1. In the case where ABPM is unavailable multiple CBP or self-measured BP can be used.

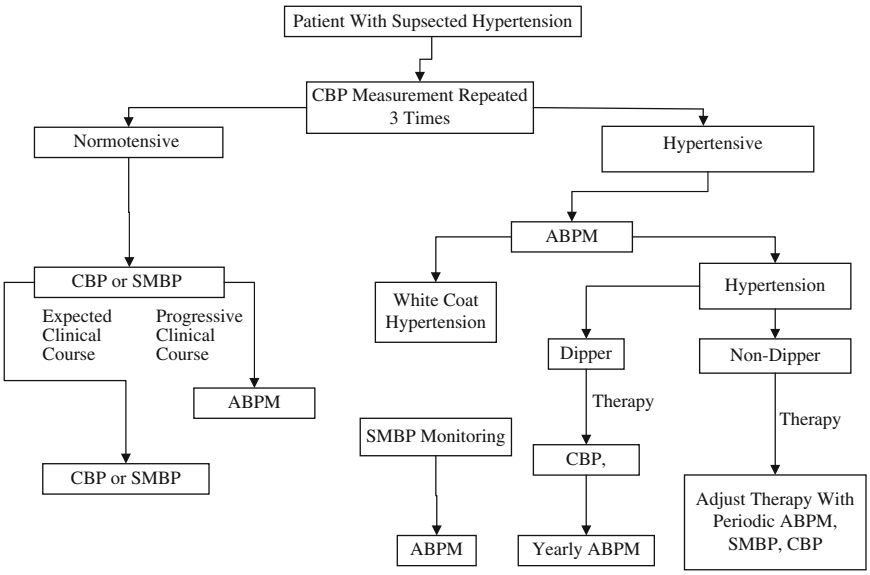

Fig. 1. When a patient is found to have an elevated BP on initial evaluation or screening, BP should be repeated at least twice. If the patient is determined to be normotensive after repeated measures, follow-up BP measurements should be taken every 6 months to a year. One must be mindful that the patient 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 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.

Phase 2: Screening for Hypertension

Why Does the Patient Have Hypertension?

The etiology of hypertension by age group is listed in Table 4. The exact percentages at each age group are unknown; however, the younger the patient and the more severe the hypertension, the more likely that the hypertension is secondary. Many adolescents have primary hypertension; however, the percentage of secondary causes in this age group remains higher than that in adults, and thus all pediatric patients must be screened for secondary causes. Renal or renovascular causes of hypertension account for ~90% of

Table 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
First year	Renovascular disease
	Renal parenchymal disease
	Coarctation of the aorta
	Iatrogenic (medication, volume)
	Tumor
Infancy to 6 years	Renal parenchymal disease
	Renovascular disease
	Coarctation of the aorta
	Tumor
	Endocrine causes[a]
	Iatrogenic
	Essential hypertension
Age 6–10 years	Renal parenchymal disease
	Essential hypertension
	Renovascular disease
	Coarctation of the aorta
	Endocrine causes
	Tumor
	Iatrogenic
Adolescence, age 12–18 years	Essential hypertension
	Iatrogenic
	Renal parenchymal disease
	Endocrine causes
	Coarctation of the aorta

[a]Shaded areas are uncommon for category.

secondary causes with 2% contributed from abnormalities of the aorta and 0.5% from pheochromocytoma *(25,26)*. 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 5) is a key starting point for the assessment of childhood hypertension; other important risk factors include metabolic syndrome and sleep-disordered breathing (either from obstructive sleep apnea or from snoring). Symptoms related to hypertension may be caused by the disease, related to the cause of the hypertension, nonspecific or absent. The newborn may

Table 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 (pseudoephedrine)
Stimulants: caffeine, ritalin, adderall
Antidepressants: tricyclics
Calcineurin inhibitors: cyclosporine, tacrolimus
Weight change
Weight loss or gain?
Time frame for interval change in weight
Weight loss as with pheochromocytoma
Weight gain as with exo- or endogenous steroids
Neonatal history: umbilical arterial catheter; neonatal asphyxia, bronchopulmonary dysplasia
Trauma
Systemic disease
Systemic lupus erythematosus
olyarteritis
Flushing, sweating, headaches, palpitations as in pheochromocytoma or neuroblastoma
Neurofibromatosis
Scleroderma
Urinary tract infections or history of unexplained or explained fevers
Substance abuse
Amphetamines
Other

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 (oral contraceptives, bronchodilators, cyclosporin, corticosteroids, decongestants, performance-enhancing substances, 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 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 still be suspected (Table 4). In older children, by contrast, secondary hypertension has a different spectrum (Table 4). The physical examination should focus on symptoms and signs of hypertension (Table 7). For all age groups with hypertension, kidney disease is a common etiology where approximately 60–90% is secondary to renal parenchymal or renovascular disease *(25,26)*. 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 examination 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 (Schwartz formula) *(27)* of glomerular filtration rate (GFR) or actual GFR measurement either by 24-h urine collection for creatinine or obtaining a formal clearance study with a marker such as iothalamate are also fundamental *(28)*. 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 non-glomerular 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 have extensive evaluation, whereas 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 make it a valued screening test. The information provided can reveal asymmetrically sized kidneys, which would suggest vesicoureteral reflux, obstruction, unilateral infection, or possible kidney

Table 6
Physical Examination: Clues to the Etiology of Hypertension

Body habitus	*Thinness*—pheochromocytoma, hyperthyroidism, renal disease (growth failure)
	Obesity—Cushing's disease
	Virilized—congenital adrenal hyperplasia
	Rickets—chronic renal disease
Skin	*Neurofibromas*—neurofibromatosis
	Café-au-lait spots—pheochromocytoma
	Tubers, ash-leaf spots—tuberous sclerosis
	Bruising—Cushing's disease, trauma
	Rashes: vasculitis—collagen vascular disease or nephritic
	Impetigo—acute nephritis
	striae—Cushing's disease
	Needle tracks—iatrogenic hypertension
Head and face	*Unusual shape*—mass lesion
	Round facies (moon)—Cushing's syndrome
	Elfin facies—William's syndrome
	Seventh nerve palsy—severe hypertension
Eyes	*EOM palsy*—nonspecific
	Fundal changes—nonspecific
	Proptosis—hyperthyroidism
Neck	*Goiter*—hyperthyroidism
	Bruit—carotid or vertebral stenosis; suggestive of fibromuscular dysplasia
Lungs	*Rales, rhonchi*—nonspecific? cardiac decompensation
Heart	*Failure*—same as for enlarged heart
	Rub—? chronic renal disease with hypertension
	Enlargement
Abdomen	*Masses*—Wilm's tumor, neuroblastoma, hydronephrosis, polycystic kidney disease
	Hepatomegaly—heart failure
	Hepatosplenomegaly—infantile polycystic disease
	Scars—GU surgery
	Bruit—renovascular disease
	Edema—renal/renovascular disease
Back/flank	*Bruit*—renovascular disease
	Flank tenderness—pyelonephritis, obstruction, acute nephritis
	Scoliosis—? hypertension secondary to renal compression
Pelvis	*Mass*—obstructive, neuroblastoma
Genitalia	*Ambiguous, virilized*—congenital adrenal hyperplasia
Extremities	*Disparity in BP, pulse, delayed refill*—coarctation
	Edema
Neurologic	*Bell's palsy*—nonspecific
	Encephalopathy—nonspecific
	Personality changes—nonspecific
	Changes in school performance–nonspecific

Table 7
Physical Signs or Symptoms Suggestive of Secondary Hypertension

Sign or symptom	*Comment*
CNS	
Hypertensive crisis	Severe hypertension with underlying encephalopathy
Bell's palsy	Often associated with severe hypertension
Hypertensive retinopathy	In children, rarely found in essential hypertension but good staging unavailable
Skin	
Neurofibromas	Pheochromocytoma/renovascular lesions
Café-au-lait spots	Pheochromocytoma/renovascular lesions
Lesions of tuberous sclerosis	Renal cysts, vascular lesions
Rash	
of systemic lupus erythematosus	Lupus nephritis
or Henoch–Schonlein purpura	Henoch–Schonlein nephritis/vasculitis
Needle tracks	Drug abuse, iatrogenic hypertension
Neck	
Goiter	Hyperthyroidism
Lungs	
Picture of bronchopulmonary dysplasia	Associated hypertension
Pulmonary edema	Volume overload associated hypertension: acute glomerulonephritis or chronic renal insufficiency
Heart	
Failure	Volume overload associated hypertension: acute glomerulonephritis or chronic renal insufficiency
Endocrine/genetic	
Multiple endocrinopathy	Pheochromocytoma
Turner's syndrome	Coarctation of the aorta
Williams syndrome	Renovascular hypertension
Van Hippel–Lindau	Pheochromocytoma
Abdominal	
Bruits	Renovascular hypertension
Enlarged kidneys	Polycystic disease, obstructive uropathy, renal inflammatory disorders (pyelonephritis, nephritis)

dysplasia, and 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 *(29,30)*.

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, and glucocorticoid remediable aldosteronism and other forms of monogenic hypertension are often associated with this electrolyte pattern and altered renin and aldosterone levels (Fig. 2) *(31)*. By contrast, elevated potassium in conjunction with a metabolic acidosis may suggest 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. Importantly, values of serum creatinine for pediatric patients differ with increasing age and often can be misinterpreted as 'normal' when in fact a significant loss of kidney mass/function has occurred despite the use of Schwartz formula *(32)*.

Syndrome	K^+	pH	Renin	Aldo	Specific Treatment	Gene Loci	Gene
GRA	↓	↑	↓	↑	Spironolactone (Amiloride, triamterene)	8q	Chimeric gene (CYP11B1/ CYP11B2)
Liddle's syndrome	↓	↑	↓	↓	Amiloride, triamterene	16p	β and γ subunit of ENaC
AME	↓	↑	↓	↓	Spironolactone (Amiloride, triamterene)	16q	11-β-HSD
MR	↓	↑	↓	↓	None, multiple drug therapy	4q	MR
Gordon's syndrome	↑	↓	↓	↓	Hydrochlorothiazide	1q 12p13 17p	WNK1 WNK4
HBS	N	N	N (↓)	N	None, multiple drug therapy	12p11	Unknown

NOTE. Contrary to the rest, the HBS is not salt sensitive and features normal values for the shown parameters.
Abbreviations: K^+, potassium; Aldo, aldosterone.
GRA: glucocorticoid-remediable aldosteronism
AME: Apparent mineralocorticord excess
MR: Mineralocorticoid receptor mutation
HBS: Hypertension brachydactyly syndrome

Fig. 2. Monogenic forms of hypertension. GRA: glucocorticoid-remediable aldosteronism; AME: apparent mineralocorticoid excess; MR: mineralocorticoid receptor mutation; HBS: hypertension brachydactyly syndrome.

What Are the Consequences of 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 et al. *(33)*. 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 of this endothelial disease marker 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 may 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 that 51% of children with primary hypertension had retinal abnormalities *(34)*. More recently, Mitchell

et al. examined children aged 6–8 years, where for every 10 mmHg increase in systolic blood pressure, a narrowing of 1.93–2.08 μm was seen in the retinal arterioles *(35)*.

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 or found to compromise cardiac function. The echocardiogram is more sensitive than the electrocardiogram for the determination of left ventricular hypertrophy/index *(36)*. ABPM has been shown to have a significant correlation to left ventricular mass 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 *(33)*. 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 *(37)*. 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 *(10–12,15,16,38,39)*. Additional markers of end-organ damage include elevated microalbumin excretion, which is especially important in, 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)*.

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, 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 Abnormality?

Phase 3 evaluation is designed to further clarify and define abnormalities identified during phase 1 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 1 is unremarkable (Table 3). 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 examination has stigmata of hyperthyroidism, e.g., weight loss, enlargement of thyroid, proptosis, we might perform a thyroid panel, but not for everyone. Individual consideration should be given to 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 for the presence of obstructive hydronephrosis. 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).

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) *(40,41)* or abdominal coarctation *(42–44)* or intracranial disease *(45)*. In our experience, Doppler ultrasound is a 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.

If other risk factors are identified, testing and/or appropriate referral should be performed. For example, glucose intolerance should be further evaluated with assessment of glycosylated hemoglobin (HgA1c), 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.

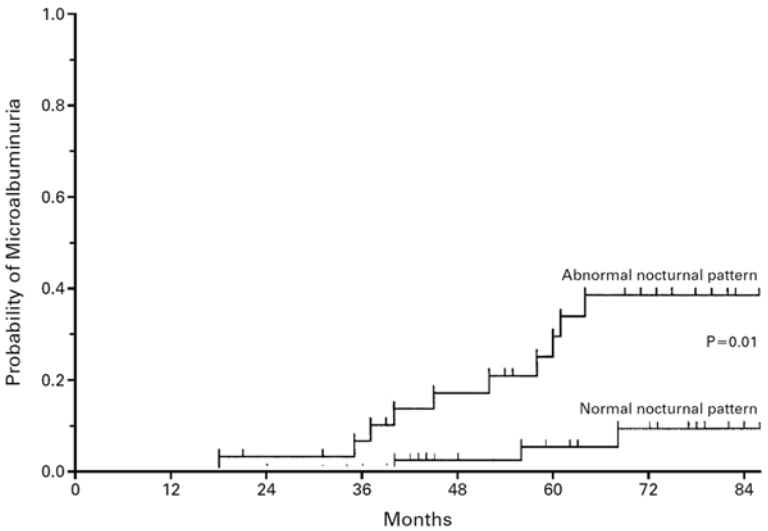

Fig. 3. Kaplan–Meier curves showing the probability of microalbuminuria according to the pattern of daytime and nighttime systolic pressure. The probability of microalbuminuria differed significantly between the two groups ($p = 0.01$ by the log-rank test; chi-square = 6.217 with 1 df). The risk of microalbuminuria was 70% lower in the subjects with a normal nocturnal pattern than in those with an abnormal nocturnal pattern *(46)*.

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 are 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 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. 3 are found, specific therapies such as amiloride or spironolactone are suggested *(47,48)*. Finding of CKD or diabetes can suggest the use of drugs affecting the renin–angiotensin system such as ACE inhibitors or angiotensin receptor blockade.

SUMMARY

While cardiovascular end points 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, e.g., 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 patients primary hypertension, (b) other risk factors for cardiovascular/kidney disease, and (c) hypertensive end-organ damage. Phase 3 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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29 The Role of Ambulatory Blood Pressure Monitoring in Diagnosis of Hypertension and Evaluation of Target Organ Damage

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Contents

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 hypertension *(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

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_29
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during both moments of activity and rest *(4)*. Indeed, over the last few years ambulatory BP monitoring has been introduced in 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 hypertension *(6)*, and it has contributed significantly to our understanding of hypertension by revealing or "unmasking" blood pressure 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 hypertension *(8)* to which now must be added masked hypertension *(9)*, a condition in which subjects classified as normotensive by conventional office or clinic measurement are hypertensive with ambulatory BP monitoring. 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 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.

Table 1
Recommendations for 24-H Ambulatory BP Monitoring *(12)*

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

Aside from the assessment of refractory hypertension or drug-induced hypotension, ambulatory BP monitoring is useful in the evaluation of white-coat hypertension and in target organ injury risk. Furthermore, ambulatory BP monitoring gives additional BP information in chronic renal failure, 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.

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 hypertension 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 hypertension. Two have values that are discrepant. The latter two are known as white-coat and masked hypertension. In sustained normotension or hypertension, both office and daytime ambulatory BP were normal and elevated, respectively. White-coat hypertension is the transient elevation of a patient's BP in response to the 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 hypertension, consists of elevated daytime or awake ambulatory BP with normal office BP *(17)*.

Besides the fact that there was higher 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 hypertension and masked hypertension, 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 hypertension are shown in Table 2.

Table 2
Studies on White-Coat and Masked Hypertension in Children and Adolescents

Author	*Population characteristics*	*Prevalence white coat (%)*	*Prevalence masked*	*Association TOD*
Sorof et al. *(16)*	71 referred subjects	31	–	–
Matsuoka et al. *(19)*	202 normo-hypertension	47	–	–
Matsuoka and Awazu *(24)*	138 normo-hypertension	–	11	–
Lurbe et al. *(17)*	592 population study	1.7	7.6	LVH in masked
Stabouli et al. *(18)*	85 referred subjects	12.9	9.4	LVH in masked
McNiece et al. *(20)*	163 referred subjects	Stage 1—34 Stage 2—15	20	LVH in masked
Kavey et al. *(21)*	119 referred subjects	52	–	LVH in white coat
Lande et al. *(22)*	217 referred subjects	31	–	–
Stergiou et al. *(23)*	102 referred subjects	18	11	–

White Coat

The prevalence of white-coat hypertension, the first of the two discrepant conditions to be recognized, differs largely among the studies published, ranging from very low values to very high values as much as 44% *(16)*, since it depends not only on the threshold selected to define hypertension 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. Sometimes the thresholds used are the same for both ambulatory and 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 hypertension clinic, reported that white-coat hypertension was present in 44 and 12.9% of the subjects, respectively. Other studies also performed in referred subjects had figures within the previously mentioned *(19–23)*. In contrast, one study which included healthy children and adolescents diagnosed only 1% to have white-coat hypertension *(17)*. This very low prevalence was not only dependent 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 hypertension, children with white-coat hypertension tended to have a higher left ventricular mass index 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 hypertension 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 hypertension 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 hypertension, 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 hypertension is predisposed to the development of sustained hypertension and has a higher left ventricular mass index with a prevalence of left ventricular hypertrophy of 22% *(20)* and 10% *(24)*.

Adolescents with persistent masked hypertension were more than twice as likely to have a parental history of hypertension. Other characteristics observed in those with masked hypertension 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 hypertension and an increase in cardiovascular risk later in life *(17)*. Parental history of hypertension, 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 hypertension even before its preceding to sustained hypertension *(25,26)*.

Because both hypertension and left ventricular hypertrophy are harbingers of adverse cardiovascular outcomes later in life *(27,28)*, masked hypertension 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 hypertension 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 hypertension. Once persistent for 1 year, masked hypertension may be an indication for BP-lowering treatment, especially in children and adolescents with a positive family history of hypertension. Whether or not pharmacological treatment should be initiated in such cases must await supporting evidence.

As for the existence of white-coat or masked hypertension 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 complementarity of ambulatory monitoring to conventional BP measurement at the office. Furthermore, a paper from Mancia and coworkers *(29)* 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 hypertension 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 hypertension, but we have to face the reality that children with masked hypertension may be seriously disadvantaged if ambulatory BP monitoring is not performed. Once masked hypertension 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 hypertension and the reverse phenomenon of masked hypertension 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 hypertension in children and

adolescents *(30)*, mainly in those at higher risk. The finding that masked and white-coat hypertension 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 *(31)*.

When to Use Ambulatory Blood Pressure Monitoring in the Diagnosis

Considering the current information above updated, ambulatory BP monitoring in children and adolescents should be performed during the process of diagnoses of hypertension in the following conditions: Confirm hypertension before starting antihypertensive drug treatment; type 1 diabetes; chronic kidney disease; and renal, liver, or heart transplant *(12)* (see Table 1).

AMBULATORY BLOOD PRESSURE MONITORING AND HYPERTENSION-INDUCED ORGAN DAMAGE

Once hypertension 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 hypertension, such as left ventricular hypertrophy 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 hypertension-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 *(31)* and the estimation of circadian variability *(32)*, a parameter that had demonstrated additional value in the evaluation of hypertension 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 left ventricular hypertrophy 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 hypertension-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) and 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 *(33)*.

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 *(34–36)*. 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 *(37–42)*. Some of these patients may experience reverse dipping, with nighttime BP exceeding daytime BP. In a study by Sorof et al. *(40)*, 72% of the patients have an attenuated decline in nocturnal systolic BP, with 24% having greater nighttime BP than daytime BP.

Even in the absence of renal insufficiency, the prevalence of the non-dipper pattern is high in such diseases as autosomic dominant polycystic kidney disease *(43)*, reflux nephropathy *(44,45)*, and type 1 diabetes *(46)*. 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 that about 58% of the microalbuminuric and 80% of the proteinuric subjects have a persistently blunted BP fall during night. The reduction in the BP nocturnal fall is independent of the disease duration *(47)*. In type 1 diabetes, the presence of persistent microalbuminuria represents an early BP dysregulation during sleep even in the absence of hypertension. When overt nephropathy is established, hypertension 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 *(48)*. 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. The potential role of sympathetic overdrive has been ruled out in a study comparing plasma norepinephrine values in dipper and non-dipper end-stage renal disease subjects *(49)*. Some authors affirm that the presence of the non-dipper pattern in subjects with end-stage renal disease depends rather on the presence of autonomic neuropathy or corticosteroid

treatment than on the end-stage renal disease itself *(50)*, although when GFR decreases, the prevalence of non-dipper pattern increases.

Whether or not 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 hypertension.

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 hypertension 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 sufficient cause to start treatment. Future studies need to be conducted to address this specific point.

Heart

The abnormal increase of left ventricular mass and/or geometry has been recognized as one of the most important markers of risk for hypertension-induced cardiovascular morbidity and mortality in adults. In children and adolescents, the relationship between hypertension and left ventricular mass 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 *(51,52)*. 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 *(53)*. In a longitudinal study, left ventricular mass tracks from early to late adolescence to about the same degree as other important risk factors, such as BP and cholesterol *(54)*. Recently, the potential role of adiposity in the increment of left ventricular mass has been highlighted. Adiposity and left ventricular mass are related in childhood, and this association tracks and becomes stronger in young adulthood. Moreover, the increase in left ventricular mass from the child to the young adult is related to the degree of increase in body mass index *(55)*.

Studies of normal and hypertensive children have found that systolic BP and left ventricular mass index 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 left ventricular mass, 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 left ventricular hypertrophy in not only healthy but also hypertensive children and adolescents. In hypertensive children, the prevalence of left ventricular hypertrophy ranges from 24 to 40% in different pediatric studies *(56–59)*.

The relationship between left ventricular mass index and systolic BP is more evident when BP is measured using 24-h ambulatory BP monitoring *(60–62)*. Consequently, hemodynamic load seems to play a more important role in the growth of left ventricular mass than previously recognized by using office BP. According to this, left ventricular mass tends to be greater in those groups with a higher ambulatory BP. In one cross-sectional study, both subjects with sustained hypertension and masked hypertensives had significantly higher left ventricular mass index than confirmed normotensive *(20)*. Moreover, in a group with adolescents who had sustained masked hypertension, left ventricular mass index 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 *(63)*, 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 *(57,64,65)*, although one study did not observe differences among normotensives and 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 *(66)*. The impact of other cardiovascular risk factors besides hypertension, 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 *(67)*. 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)*. Up to now, the information about the relationship between carotid wall thickness and ambulatory BP came from only two studies in obese children. While in one of them *(68)* no relationship between carotid wall thickness and ambulatory BP was observed, the other provided strong evidence that carotid intima-media thickness is increased in childhood primary hypertension independent of the effect of obesity *(69)*.

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30 Nonpharmacologic Treatment of Pediatric Hypertension

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Contents

INTRODUCTION

During childhood, elevated systolic and/or diastolic blood pressure (BP) is commonly secondary to diseases of the kidneys, endocrine system, and/or cardiovascular system. When diagnostic evaluation does not reveal a cause for the elevation in BP, the condition is referred to as essential, or idiopathic, hypertension (HTN). Over 90% of HTN in adults is essential HTN; there are well over 60 million Americans with essential HTN. Much has been written about research to control essential HTN in adults; relatively less work has been done concerning children. Many pharmacologic approaches, such as β (beta)-blockade, angiotensin-converting enzyme (ACE) inhibition, afterload reduction, and α (alpha)-blockade, have been successful in lowering BP. When essential HTN occurs in childhood, a nonpharmacologic approach to lowering BP is preferable so that the patient may not require lifelong medication. Long-term use of medications may be associated with significant side effects and produce associated morbidity and/or mortality.

Several nonpharmacologic approaches have been successful in lowering BP in adults and children. These include weight loss, exercise, stress reduction, and alterations in electrolyte intake, in particular Na^+, K^+, and Cl^-. Chapter 15, by Dr. Wilson, discusses the effects of dietary electrolytes on BP. Chapter 17, by Dr. Rocchini, provides evidence that weight loss may control essential HTN. These findings will not be repeated in this chapter. The

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_30
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specific areas covered herein are exercise and stress reduction. More research is needed in both areas.

EXERCISE

Several years ago, Alpert and Wilmore *(1)* published a review of data relating to the effects of activity/exercise on BP in healthy children and adolescents, as well as in those with elevated BP. If BP was normal prior to the exercise intervention, there was no measurable change in systolic (S) BP or diastolic (D) BP after the program. At the time of that review, there were seven studies that reported data relating to changes in BP in children and adolescents with essential HTN in response to an exercise/activity intervention. An extensive literature review by one author failed to find additional, recent studies addressing this issue.

The first documented research concerning exercise was an abstract in 1979 by Laird et al. *(2)*. They studied seven boys, aged 15–16 years. The intervention was a 2-month program of weight lifting, presumably both an aerobic and an isometric activity. They measured SBP, DBP, and left ventricular (LV) mass. The change in SBP was small, from a mean of 134 to 131 mmHg. The inclusion criteria of essential HTN identified in these subjects, whose SBP prior to the intervention was only 134 mmHg, weaken the value of the study somewhat. The DBP change from pre- to postexercise was from a mean of 78 to 80 mmHg. A similar, insignificant change in LV mass occurred, from 198 to 202 g. The important conclusion from this abstract was that resistance training did not lead to an increase in BP, which had been thought of as a possibility. The authors concluded that "hypertensive" youth did not need to be restricted from resistance training.

Shortly thereafter, Frank and coworkers *(3)* reported data from the Bogalusa Heart Study on 48 children (gender unspecified) from 8 to 18 years of age whose BPs were in the top decile of a group of 1604 youth followed in that study. The subjects were receiving antihypertensive medications. The intervention included both dietary and exercise components; the exercise component was not rigorously described. The intervention was successful, lowering both SBP and DBP by 9 mmHg each. Because the patients had dietary, exercise, and pharmacologic treatments simultaneously, no conclusions may be drawn as to the effectiveness of exercise alone in this group of Caucasians and African-Americans.

In 1983 and 1984, Hagberg and colleagues *(4,5)* published two articles from studies in 25 children, 19 of whom were boys. The mean age was 15.6 years, and all attended public schools. There were 6 African-Americans and 19 Caucasians. A control group was included, rendering these findings statistically more robust. The subjects underwent a 3-day/week, 30–40-min/day aerobic program supervised by school physical education faculty. The subjects were identified as hypertensive through carefully performed screenings. The variables measured prior to the 6-month training period and after 9 months of detraining included SBP, DBP, and VO_2 max. The study results are summarized in Table 1. The effects of the program were more pronounced in boys compared to girls; the mixed-gender control group experienced no training-induced changes. There were no racial differences. The positive changes were all reversed with detraining. This small controlled trial supports the hypothesis that aerobic exercise lowers BP in adolescents with essential HTN. The expected drops in BP should be approximately 8 mmHg for SBP and 5 mmHg for DBP.

The Hagberg team *(6)* expanded their studies by utilizing an aerobic program followed by weight training. There were 6 children in the treatment group and 17 controls. The aerobic program consisted of 5 months of endurance training (running) at 60–75% of VO_2

Table 1
Hagberg et al. *(4,5)* Study Results

Condition	*Systolic BP (mmHg)*	*Diastolic BP (mmHg)*	*VO_2 max (mL/kg/min)*
Pretraining	137	80	43
End of training	129*	75*	48
Detraining	139	78	43

*$p < 0.01$.

max. Each session lasted 30–50 min and occurred 3 days/week. After the aerobic training phase, the youths switched to a weight training program consisting of 12–15 repetitions of 14 exercises. That phase also lasted 5 months. The subjects then detrained for 12 months. The SBP fell from 143 to 130 mmHg following the aerobic sessions and to 126 mmHg at the end of the endurance training. After detraining it rose to 142 mmHg. The changes with exercise were of statistical significance. The parallel changes of DBP were from 80 to 77, 73, and 74 mmHg, none of which were statistically significant. There were decreases in measured systemic vascular resistance in response to both endurance and weight training. These studies continue to support the concept that both endurance and weight training have beneficial effects on SBP and, to a lesser degree, DBP in youth with essential HTN. The group of six children was too small to draw conclusions with respect to either gender or ethnicity.

More recently, Danforth et al. *(7)* used a simple cycle ergometer or jogging/walking program in a group of 12 African-American children (mean age 11.5 years) of low socioeconomic status. The sessions were 30 min/day, 3 days/week for 12 weeks. The target intensity was 60–80% of maximal heart rate (HR). The results are shown in Table 2. The intervention led to a 9 mmHg reduction in SBP and a 9 mmHg decrease in DBP, both of which were statistically significant. The DBP returned to baseline after detraining; however, there was a lasting effect of the reduction after detraining for SBP. The compliance (attendance) was an outstanding 96%. The decrease in BP was not related to a change in weight. This study shows that inexpensive programs may yield results similar to those involving more expensive equipment or which last more than 3 months.

The final study on which we comment comes from a very productive research team in Denmark *(8)*. The Odense Schoolchild Study has produced numerous significant results. In this particular publication, results from 137 children (68 normotensives and 69 hypertensives) were reported. The children were 9–11 years of age. The 8-month intervention involved three additional 50-min sessions of school physical education per week. The

Table 2
Danforth et al. *(7)* Study Results

Condition	*Systolic BP (mmHg)*	*Diastolic BP (mmHg)*
Initial	130	84
Posttraining	121*	75*
Detraining	123*	85

*$p < 0.01$ vs initial.

variables reported were SBP, DBP, and VO_2 max. The SBP in the "hypertensive" boys decreased from 113 to 107 mmHg ($p < 0.05$). No significant change occurred in the DBP values. There was a slight but significant increase in VO_2 max, 52–54 mL/min/kg. No statistically significant changes in SBP or DBP occurred in the hypertensive girls. During the 8-month study, data were collected at 3 months to assess interval changes; none occurred. The significant results all occurred at the end of the 8-month period. This is the largest series published to date and concludes that boys appear to benefit more than girls from an intensive exercise intervention.

In summary, endurance (aerobic) exercise led to reductions of SBP and DBP, but seldom to completely normal levels. The "hypertensives" generally did not have BP elevations much greater than the normotensive/hypertensive cutoffs. The one study that used only resistance training *(2)* did not show a reduction in BP, but when resistance training was performed following an aerobic program, the reductions in BP were maintained. There has been a concern that children with essential HTN should not participate in resistance training. No study showed a deleterious effect. Accordingly, we do not believe that children with essential HTN who do not show evidence of end-organ damage such as stroke, renal failure, or increased LV mass need to be excluded from resistance training.

From available data, it is not possible to state what is the minimal frequency, intensity, or duration of exercise that will lead to reductions of SBP or DBP. From a public health standpoint, exercise should be lifelong in duration. Recent recommendations *(1)* have been for three or more sessions per week, 30 or more minutes per day, and at least at 60% VO_2 max.

Future studies should enroll children with more severe elevations of BP. Children of all ethnicities should be included. The reason for the apparently better results in male, compared to female, children needs to be investigated. For optimal efficiency these studies should be multicenter. An organization such as the North American Society for Pediatric Exercise Medicine could be a valuable resource for such a study. We hope that the readers of this chapter will appreciate the paucity of rigorous data and will seek to provide future studies to define the much needed data.

STRESS REDUCTION

The relevance of stress reduction for the treatment of essential HTN dates back to early theories regarding the pathogenesis of the disorder. Clinical and empirical data implicate stress as an important factor for the development and maintenance of HTN in certain persons and provide a rationale for the use of stress management techniques in at-risk persons. With respect to children and adolescents, such nonpharmacologic approaches are especially important, since elevated BP in childhood often relates to essential HTN in early adulthood, and clinical trials have not conclusively determined the long-term risk–benefit ratio of antihypertensive drug therapy for youth *(9)*. Consequently, current guidelines for treating childhood HTN are conservative; when essential HTN is the likely diagnosis in the context of mild BP elevations, interventions that emphasize lifestyle or health-promoting behavioral changes are recommended.

In general, nonpharmacologic therapies for essential HTN encompass strategies aimed at weight reduction, dietary modification, and physical activity. Considerably less attention has been devoted to stress reduction, per se; this disparity is even more apparent for pediatric HTN patients. This is surprising given the effectiveness of stress reduction techniques such as biofeedback and relaxation training for a variety of medical conditions affecting

children, including fecal *(10)* and urinary *(11–13)* incontinence, headache *(12,13)*, and asthma *(14)*. One possible explanation for the lack of carryover may be the relatively recent incorporation of BP measurement in the routine pediatric examination *(9)*. Reluctance on the part of some physicians to inquire about recreational behaviors (e.g., drinking, smoking) that may have negative overall effects on young patients *(15)* also may contribute to a lack of perceived need for more formal treatment recommendations that emphasize stress reduction in children and adolescents with essential HTN.

Research has demonstrated that stress elicits significant increases in BP and other hemodynamic parameters in children. Furthermore, a number of studies have shown that these BP responses to stress predict future elevations in resting BP in children and adolescents over periods of several months to years *(16–22)*. Consequently, the utilization of techniques to reduce reactivity to stress during childhood may prevent the development of essential HTN across the life span.

Two studies provide some support for the use of stress reduction in children at risk for developing essential HTN *(23,24)*. Utilizing nonsomatic therapies, these studies reported substantial changes in BP, or behaviors associated with elevated BP, in disparate samples of children. Although the lasting effects of these interventions are not known, these studies underscore the importance of stress and stress reduction in childhood HTN.

The first investigation examined the effects of Medical Resonance Therapy Music (MRT-Music) in a sample of children with transient HTN following the nuclear accident in Chernobyl *(23)*. Sixty children with varying degrees of BP elevation were exposed to twice-daily MRT-Music treatments for 3 weeks while in the hospital. Treatment sessions lasted 20–30 min and occurred under conditions designed to maximize relaxation. Pre- and post-treatment comparisons of basic hemodynamic parameters revealed a strong treatment effect for both SBP and DBP, with a normalization of overall BP to age-appropriate levels. This effect was particularly pronounced for those children with higher, compared to lower, levels of HTN at the onset of treatment.

The second study examined the relationship between religion and various parameters of cardiovascular (CV) health in a sample of 137 immigrants between 18 and 71 years of age *(24)*. Regression analyses indicated strong associations among demographic, social support, and physical health measures for this group of individuals deemed to be at risk for BP elevations secondary to immigration-related stress. After ruling out a number of competing explanations for the observed relationships, the author concluded that religious commitment had a beneficial effect on CV health, as indicated by significantly lower rates of HTN, as well as significantly lower SBP and DBP levels among those high on both quantitative and qualitative indices of religious commitment. This association was particularly strong for younger persons in the sample. The author discussed this relationship in terms of social support and noted that religious participation appeared to remove a source of stress among immigrants by facilitating feelings of social cohesion and a sense of belonging. Although over one-third of the sample was classified as hypertensive, it is unclear how many participants were adolescents, as opposed to adults. Nevertheless, the study provided support for the positive effects of church attendance and religious commitment on CV health in general and BP elevations in particular, among both youthful and older immigrants.

Four studies of nonpharmacologic stress reduction treatments for normotensive children have implications for the management of childhood HTN. One study evaluated the effects of gender and family support on dietary compliance and BP in a sample of 184 African-American adolescents who participated in a 5-day low-Na+ diet as part of a HTN prevention program *(25)*. Compliance was defined as urine Na+ excretion $\leq$50 mEq/24 h at the

completion of the dietary intervention. A trend toward lower SBP was observed among compliant participants, but the effect diminished after controlling for body mass index. Moreover, dietary compliance was moderated by social support and gender. These findings suggest that social support may play a role in improving dietary compliance and, subsequently, BP control among adolescents at risk for developing essential HTN.

Another study evaluated the impact of transcendental meditation (TM) at rest and during acute psychological stress in high school students *(26)*. Adolescents with high-normal BP were randomly assigned to either a TM or a health education control group. Pre- and postintervention comparisons revealed significant group differences, with TM participants exhibiting greater decreases in resting SBP and greater declines in SBP during a car driving simulation task compared to control group peers.

In contrast, generally unfavorable results have been reported for the use of progressive muscle relaxation (PMR) in the treatment of adolescents with high BP *(27,28)*. Compared to wait-list controls, significant declines in SBP were observed in teenagers upon completion of a 3-month school-based PMR program. At follow-up 4 months later, however, group differences in BP were no longer significant *(27)*. Similarly, 4 months of relaxation training, combined with increased physical activity, failed to yield BP differences in comparisons of community boys with nontreated peers *(28)*.

SUMMARY

Given the link between elevated BP during childhood and the development of adult HTN, the need for interventions aimed at reducing disease development in at-risk youth is apparent. Stress has been identified as an important contributor to the progression and maintenance of HTN in certain individuals. Nonpharmacologic techniques that minimize stress to achieve and maintain normal BP are particularly relevant for children because clinical trials have not conclusively determined the long-term risk–benefit ratio of antihypertensive drug therapy for young patients. When essential HTN is the likely diagnosis in the context of mild BP elevations in children and adolescents, interventions that emphasize lifestyle or health-promoting behavioral changes are recommended *(9)*. Stress reduction is an example of such an approach. In addition to using stress reduction techniques to treat children with essential HTN, these methods may be useful for children with high-normal BP and may provide adjunctive benefit to more intensive therapies for young patients with severe disease.

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31 Pharmacotherapy of Pediatric Hypertension

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Contents

Hypertension is the primary cause of cardiovascular disease in humans. In adults, hypertension is clearly linked to an increased risk of stroke, ischemic heart disease, congestive heart failure, and kidney disease *(1)*. Fortunately, the devastating cardiovascular health outcomes seen in the adult population are infrequently seen in children, but the seemingly benign nature of hypertension in children may be more a result of the duration of exposure rather than any disease, developmental, or physiologic factor. Emerging evidence suggests that the pathophysiology of cardiovascular disease and resultant adverse health outcomes begins during childhood and, if left unattended, will likely culminate in the clinical presentation of cardiovascular disease as an adult. The evidence pointing to a pediatric onset of adult cardiovascular disease includes the finding of left ventricular hypertrophy (LVH) and increased carotid intimal–medial thickness (cIMT) in many children with hypertension *(2–6)*, as well as epidemiologic studies finding an association between cardiovascular disease as an adult and high blood pressure readings as a youth *(7–10)*.

Compared to adults where normal blood pressure is defined based on the risk of adverse health outcomes, hypertension in children and adolescents is based on the normative

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_31
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distribution of BP in healthy children and adolescents and is defined as average systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) that exceeds the 95th percentile for gender, age, and height on repeated occasions *(11)*. Those children not meeting the criterion for hypertension but potentially at risk for developing hypertension or hypertensive-related cardiovascular disease (e.g., "pre-hypertension") are defined as children and adolescents with average SBP and/or DBP between the 90th and 95th percentile for gender, age, and height or BP levels greater than 120/80 mmHg. In the general population the prevalence of hypertension in children and adolescence is approximately 1–4% *(12)*. The prevalence of "pre-hypertension" has not been clearly delineated but is likely substantial. The prevalence of hypertension in children with chronic kidney disease, solid organ transplantation, and obesity is greatly increased and at times may occur in up to 70% of the at-risk population *(13)*.

Adequate control of blood pressure in adults, irrespective of the means by which the blood pressure is lowered, reduces the rate of cardiovascular mortality, stroke, and congestive heart failure events *(1)*. While there can be concomitant conditions associated with HTN that are compelling indications for the use of a particular antihypertensive agent, such as the desire to prescribe an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor antagonist (ARB) in a patient with proteinuric chronic kidney disease (CKD) or diabetes mellitus (DM) due to the additional renoprotective effect independent of the reduction in blood pressure *(14–16)*, there appears to be similar protection against cardiovascular disease among the different classes of antihypertensive agents when adequately titrated to achieve desired BP goal. With this in mind, the current emphasis in the treatment of hypertension is not focused on which of the numerous and often redundant antihypertensive drugs should be selected, but rather on using a sufficient amount of drug or drugs to control BP. In response to the 1997 Food and Drug Administration Act and the 2002 Best Pharmaceuticals in Children Act that provided patent extensions in return for pediatric studies, a number of antihypertensive agents have been evaluated in children providing some limited information on the safety and effectiveness of antihypertensive agents in children with hypertension. While the recent influx of information is encouraging, there continues to be gaps between the extent of pediatric-specific information that is available and what is needed to make rationale therapeutic decisions about the pharmacologic treatment of the hypertensive child. Specifically, there is a great need for individual and comparative studies evaluating the effect of antihypertensive agents on long-term health outcomes or biological markers of cardiovascular disease (e.g., LVH, cIMT) in children with hypertension.

In the absence of objective information on the long-term health risks of hypertension in children and adolescents and on the impact of lifestyle or pharmacologic interventions on clinically significant outcome measures, the decision to begin pharmacologic therapy in children with high blood pressure is arbitrary. Most experts seem to agree that pharmacologic therapy should be strongly considered in children with symptomatic hypertension, concomitant chronic kidney disease, or diabetes mellitus and in those children demonstrating hypertensive target-organ damage (e.g., LVH, cIMT, retinopathy). Less clear is when to initiate pharmacologic therapy for the asymptomatic child with persistent hypertension that has not responded to a trial of lifestyle modifications or the asymptomatic child that has other cardiovascular risk factors such as obesity, sleep apnea, or lipid abnormalities. In the absence of evidence, a common approach is to consider adding a pharmacologic agent to the treatment regimen after a 6–12-month trial of lifestyle modification.

PRINCIPLES OF ANTIHYPERTENSIVE THERAPY

Any child that consistently has blood pressure measurements exceeding 90% for age, gender, and height when measured with the appropriate techniques *(11)* warrants some form of intervention, and therapeutic lifestyle changes are an important component of treatment in all children and adolescents with elevated BP irrespective of the plan to initiate pharmacologic therapy. In some children blood pressure may be adequately controlled by a combination of weight reduction (in overweight children), regular physical activity, and the ingestion of a diet rich in fruits and vegetables and low in salt (i.e., the Dietary Approaches to Stop Hypertension or DASH diet) *(17)*. The potential for normalization of blood pressure with time in children with presumed hypertension was noted in a pediatric study where 17% of hypertensive children enrolled in an antihypertensive drug trial had normalization of their blood pressure during the 2-week placebo screening period and 34% of children randomized to placebo had normalization of blood pressure during the 12-week study *(18)*. Although therapeutic lifestyle changes may not result in adequate control of BP, the principles should continue to be emphasized upon the introduction of antihypertensive drugs as continuance of therapeutic lifestyle changes may facilitate the pharmacologic control of blood pressure. In addition, the successful and continued implementation of therapeutic lifestyle changes may have an ongoing and progressive effect on blood pressure (e.g., continued weight loss or improved physical conditioning) that may permit the withdrawal of the pharmacologic support with time.

Antihypertensive drugs lower BP by altering one of the physiologic components responsible for arterial pressure, namely cardiac output and peripheral vascular resistance. At its core, the therapeutic actions of BP lowering for all antihypertensive drugs result from their ability to either lower peripheral vascular resistance, reduce cardiac output, or both. Peripheral vascular resistance can be reduced through direct relaxation of the smooth muscle in the resistance vessels or indirectly by interfering with the effector signals of one of the many systems, such as the sympathetic nervous system or renin–angiotensin–aldosterone system, that cause constriction of resistance vessels. A reduction in cardiac output may be achieved by a decrease in myocardial contractility or a decrease in the ventricular filling pressure that may accompany a change in venous pressure or blood volume. A classification of antihypertensive drugs by the primary mechanism of action is shown in Table 1. As BP is maintained by a complex, coordinated, and often overlapping set of regulatory systems, drug-induced lowering of blood pressure that occurs by interference with one component of the regulatory system (e.g., vasodilation) often results in a reactive change in another component of the regulatory system (e.g., tachycardia, enhanced salt, and water reabsorption) that counteracts or blunts the blood pressure-lowering effect. For this reason, the use of more than one drug with a different mechanism of action is often required to effectively lower blood pressure. While there may be formulation and dosage concerns when applied to children, the pharmaceutical industry has long recognized the blood pressure-lowering benefits of combining treatment with different classes of antihypertensive agents and has marketed several combination products (Table 4).

To date, the antihypertensive drug trials that have been completed in children and adolescents have shown that a variety of antihypertensive agents are capable of lowering blood pressure in children with hypertension. While helpful, the information from these studies is limited by the small number of patients treated during the clinical trials, the short duration of therapy, and lack of meaningful health outcome end points. Likewise, comparative studies of antihypertensive agents in children have not been completed.

Table 1
Classification of Antihypertensive Drugs and Mechanism of Action

Drug classification	*Primary mechanism of action*
Angiotensin-converting enzyme inhibitors	Decreases angiotensin II-induced constriction of resistance vessels
Angiotensin II receptor antagonist	Blocks angiotensin II-induced constriction of resistance vessels
Calcium channel blockers	Decreases constriction of resistance vessels
Diuretics 1. Thiazide and thiazide-like agents 2. Loop diuretics 3. Potassium sparing	Reduces ventricular filling pressure by volume reduction. Long-term use results in decreased vascular resistance
Renin inhibitors	Decreases angiotensin II-induced constriction of resistance vessels
Sympatholytic drugs 1. α-Adrenergic antagonist 2. β-Adrenergic antagonist 3. Mixed adrenergic antagonist 4. Centrally acting agents 5. Adrenergic neuron-blocking agent	Reduces cardiac contractility and/or decreases constriction of resistance vessels
Vasodilators	Decreases constriction of resistance vessels

Due to the heterogeneous nature of childhood hypertension with a high rate of secondary causes, especially in the young child, most practitioners have abandoned the indiscriminant stepped-care approach for an individualized approach to antihypertensive drug therapy *(19)*. With an individualized approach, the initial antihypertensive drug is chosen based on the presumed mechanism and severity of hypertension; concomitant diseases and therapies; availability of appropriate formulations (e.g., suspension and dosage choices); and, when available, pediatric safety, pharmacokinetics, and efficacy data. In general, individualized therapy begins with a low dose of the initial drug (Table 5) and is slowly titrated upward, based on the blood pressure response or side effects. Unless clinically warranted, dose titration should proceed slowly, especially with antihypertensive drugs that have a long biological half-life (e.g., amlodipine), so that the blood pressure response at each dose level can be fully evaluated. An alternative antihypertensive agent can be substituted if no response or significant side effects are observed (Table 2). A second drug is added to the current regimen if the response to the first drug is inadequate but well-tolerated and correctable causes of an inadequate response are addressed (Table 3). When a second agent is needed for blood pressure control, diuretics appear to be the most useful as they have been shown to have an additive blood pressure-lowering effect when added to other classes of antihypertensive agents. If blood pressure is controlled with a second drug, a fixed combination preparation can be substituted if the appropriate dosing formulation is available (Table 4). Once blood pressure is controlled for 6–12 months and target-organ damage has regressed or resolved, an effort to decrease the dosage or number of antihypertensive medications should be considered. Lifestyle modifications are maintained during step-down therapy and

Table 2
Clinical Problems with Antihypertensive Drugs

ACE inhibitors/AT II receptor antagonist
Use with caution in patients with bilateral renal artery stenosis or renal artery stenosis in a solitary kidney
Use during pregnancy associated with fetal and neonatal toxicity
Cough, hypotension, angioedema, renal failure, hyperkalemia, neutropenia
Renin inhibitors
Angioedema, hyperkalemia, diarrhea (high dose)
Calcium channel blockers
Profound and unexpected drops in BP seen with short-acting nifedipine
Flushing, headache, fatigue, palpitations, edema
Vasodilators
Fluid retention, edema, palpitations
Minoxidil—hypertrichosis
Hydralazine—lupus-like syndrome (greater in slow acetylators)
β-Adrenergic antagonists
Use with caution in patients with bronchial asthma, heart failure, diabetes mellitus
Fatigue, cold extremities, sedation, bradycardia, abnormalities of lipid and glucose metabolism
Peripheral α-adrenergic antagonist
Orthostatic hypotension with "first-dose effect"
Centrally acting α-adrenergic agonist
Rebound hypertension with abrupt withdrawal
Sedation, dry mouth, headache
Diuretics
Potassium loss, volume depletion
Hearing loss (loop diuretics), hyperkalemia (potassium-sparing diuretics)

Table 3
Causes of Inadequate Response to Antihypertensive Therapy

Inappropriate measurement technique
Damaged/improperly calibrated equipment
Noncompliance with prescribed therapy
Medication noncompliance
Dietary noncompliance (e.g., low salt, fluid restriction)
Lifestyle modification noncompliance (failure to lose weight, exercise, . . .)

Table 3
(continued)

Progression of underlying disease
Worsening renal failure
Arteritis/vasculitis
Inappropriate drug for underlying mechanism of HTN
Dose of antihypertensive medications too low
Drug interactions
Sympathomimetics, illicit drugs
Caffeine
Oral contraceptives, corticosteroids, cyclosporine, tacrolimus
NSAIDs
Drug metabolism
Rapid inactivation (e.g., rapid acetylator with hydralazine)
Slow bioactivation of prodrug (e.g., losartan, irbesartan)
Other undefined pharmacogenetic variant (e.g., sodium channel mutation)

Table 4
Antihypertensive Fixed-Drug Combinations (Products Available in USA)

Drug	*Formulation*	*Cost/day*
ACE inhibitors (+) diuretics		
Benazepril (+) HCTZ	5 mg/6.25 mg; 10/12.5; 20/12.5; 20/25	$1.05
Captopril (+) HCTZ	25 mg/15 mg; 50/15; 25/25; 50/25	$0.72
Enalapril (+) HCTZ	5 mg/12.5 mg; 10/25	$1.19
Lisinopril (+) HCTZ	10 mg/12.5 mg; 20/12.5; 20/25	$1.34
Moexipril (+) HCTZ	7.5 mg/12.5 mg; 15/12.5; 15/25	$1.38
Quinapril (+) HCTZ	10 mg/12.5 mg; 20/12.5; 20/25	$1.22
ACE inhibitors (+) CCBs		
Benazepril (+) amlodipine	10 mg/2.5 mg; 10/5; 20/5	$3.56
Trandolapril (+) verapamil ER	1 mg/240 mg; 2/180; 2/240; 4/240	$3.27
AT II receptor antagonists (+) diuretics		
Candesartan (+) HCTZ	16 mg/12.5 mg; 32/12.5	$3.16
Eprosartan (+) HCTZ	600 mg/12.5 mg	$3.44
Irbesartan (+) HCTZ	150 mg/12.5 mg; 300/12.5; 300/25	$3.13
Losartan (+) HCTZ	50 mg/12.5 mg; 100/12.5; 100/25	$2.60

Table 4
(continued)

Drug	*Formulation*	*Cost/day*
Olmesartan (+) HCTZ	20 mg/12.5 mg; 40/12.5; 40/25	$3.06
Telmisartan (+) HCTZ	40 mg/12.5 mg; 80/12.5; 80/25	$2.57
Valsartan (+) HCTZ	80 mg/12.5 mg; 160/12.5; 160/25; 320/12.5; 320/25	$2.80
AT II receptor antagonist (+) CCBs		
Olmesartan (+) amlodipine	20 mg/5 mg; 20/10; 40/5; 40/10	$3.06
Valsartan (+) amlodipine	160 mg/5 mg; 160/10; 320/5; 320/10	$3.53
AT II receptor antagonist (+) CCBs (+) diuretic		
Valsartan (+) amlodipine (+) HCTZ	160 mg/5 mg/12.5 mg; 160/5/25 160/10/12.5; 160/10/25; 320/10/25	$3.13
Renin inhibitor (+) diuretic		
Aliskiren (+) HCTZ	150 mg/12.5 mg; 150/25; 300/12.5; 300/25	$2.82
β-Adrenergic antagonist (+) diuretics		
Atenolol (+) chlorthalidone	50 mg/25 mg; 100/25	$0.90
Bisoprolol (+) HCTZ	2.5 mg/6.25 mg; 5/6.25; 10/6.25	$1.14
Propranolol (+) HCTZ	40 mg/25 mg; 80/25	$0.53
Metoprolol (+) HCTZ	50 mg/25 mg; 100/25; 100/50	$1.80
Vasodilators (+) diuretics		
Hydralazine (+) HCTZ	25 mg/25 mg; 50/50;	$1.56
Sympatholytics (+) diuretics		
Clonidine (+) chlorthalidone	0.1 mg/15 mg; 0.2/15; 0.3/15 1 mg/0.5 mg; 2/0.5; 5/0.5	$1.22
Diuretics (+) potassium-sparing diuretics		
HCTZ (+) spironolactone	25 mg/25 mg; 50/50	$0.50
HCTZ (+) triamterene	25 mg/37.5 mg; 25/50; 50/75	$0.35
HCTZ (+) amiloride	50 mg/5 mg	$0.42

HCTZ: hydrochlorothiazide.
Cost/day: based on average AWP and initial adult dosing recommendations.

drug reductions should be made methodically and slowly in order to fully assess the blood pressure response with each change.

There are clinical situations where a specific class of drug has proven more effective or beneficial for reasons independent of blood pressure lowering *(20,21)*. In the child with diabetes mellitus and microabluminuria or proteinuria, an ACE inhibitor is recommended as ACE inhibitors have been shown to slow the loss of renal function in adults with diabetic proteinuric renal disease *(14)*. Although outcome studies have not been performed with angiotensin II (AT II) receptor antagonists, these agents may also be beneficial for patients in whom ACE inhibitors are indicated, but the patients are unable to tolerate ACE inhibitors. ACE inhibitors are also recommended for children with proteinuric kidney disease or chronic kidney disease. The loss of kidney function in adults with proteinuric kidney disease is slowed in those receiving ACE inhibitors *(15,22,23)*.

In the absence of an absolute indication for a specific antihypertensive drug, the trend in the treatment of hypertension in children has been the use of ACE inhibitors, long-acting dihydropyridine calcium channel blockers (CCBs), and AT II receptor antagonists. These agents have gained favor due to the low side-effect profile, long duration of action requiring once- or twice-daily dosing, and the availability of formulations that allow for pediatric dosing. However, the use of agents that interfere with the angiotensin system in girls of childbearing potential is tempered by the potential fetal and neonatal adverse effects. For many of the newer antihypertensive drugs, pharmacokinetic and efficacy studies have been completed providing for the rational use of these agents in children. Although many of the traditional agents are still available for use in children with hypertension, it is unlikely that efficacy and pharmacokinetic studies will be performed and the pediatric dosing information will continue to be based on the reported experience in a few patients. Other antihypertensive agents that may be reasonably used as first-line agents include thiazide-type diuretics, β-adrenergic antagonists, and peripheral ∝–adrenergic antagonists. The ∝-adrenergic antagonists such a doxazosin, prazosin, and terazosin may be useful in the obese adolescent with "insulin-resistant syndrome" due to the minimal effect of the drug on lipid and carbohydrate metabolism and the reported enhanced sympathetic activity in such patients *(24,25)*. Vasodilators (e.g., hydralazine, minoxidil) and central ∝-adrenergic agonists (e.g., clonidine, guanfacine) are to be considered second-line agents. The role of the newest class of antihypertensive medications, renin inhibitors, in the treatment of pediatric hypertension is yet to be determined. See Table 5 for dosing recommendations.

Angiotensin-Converting Enzyme (ACE) Inhibitors

Angiotensin-converting enzyme catalyzes the conversion of angiotensin I to angiotensin II, which in turn influences blood pressure by direct vasoconstriction of the arterial vasculature, increased sympathetic nervous system activity, direct cardiovascular inotropic effect, and aldosterone-enhanced salt and water retention. ACE inhibitors, such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril, reversibly inhibit the enzyme and block the formation of angiotensin II and the degradation of the vasodilatory peptide bradykinin.

Because renal and renovascular diseases are frequent causes of childhood hypertension, ACE inhibitors are commonly prescribed. ACE inhibitors are well tolerated by children and lower blood pressure in hypertensive children in a dose-dependent manner *(26–34)*. Neonates appear to be extremely sensitive to the blood pressure-lowering effects of ACE

Table 5
Suggested Dosing of Antihypertensive Medication in Children and Adolescents

Drug	*Pediatric dosing*	*Adult dosing*	*Formulation*	*Cost/day*
ACE inhibitors				
Benazepril[R]	Initial: 0.2 mg/kg QD Max: 0.6 mg/kg/day [40 mg/day]	Initial: 10 mg/day Max: 80 mg/day	T: 5 mg/10/20/40 Extemp: 2 mg/ml	$1.05
Captopril[R]	Initial: 0.2–0.5 mg/kg Q 6–12 h or 12.5–25 mg/dose BID/TID Max: 6 mg/kg/day	Initial: 25 mg BID/TID Max: 450 mg/day	T: 12.5 mg/25/50/100 Extemp: 1 mg/ml	$1.50–2.25
Enalapril[R]	Initial: 0.08 mg/kg QD Max: 0.6 mg/kg/day [40 mg/day]	Initial: 2.5–5 mg QD Max: 40 mg/day	T: 2.5 mg/5/10/20 Extemp: 1 mg/ml	$1.02
Fosinopril[R]	Initial: 0.1 mg/kg QD Max: Not established	Initial: 10 mg QD Max: 80 mg/day	T: 10 mg/20/40	$1.19
Lisinopril[R]	Initial: 0.07 mg/kg QD [5 mg/day] Max: 0.6 mg/kg/day [40 mg/day]	Initial: 10 mg QD Max: 80 mg/day	T: 2.5 mg/5/10/20/30/40 Extemp: 1 mg/ml; 2 mg/ml	$0.99
Moexipril[R]	No data	Initial: 7.5 mg QD Max: 60 mg/day	T: 7.5 mg/15	$1.38
Perindopril[R]	No data	Initial: 4 mg QD Max: 16 mg/day	T: 2 mg/4/8	$2.56
Quinapril[R]	Initial: 0.1–0.2 mg/kg QD [5–10 mg QD] Max: No information	Initial: 10 mg QD Max: 80 mg/day	T: 5 mg/10/20/40	$1.22
Ramipril[R]	No data	Initial: 2.5 mg QD Max: 20 mg/day	C/T: 1.25 mg/2.5/5/10	$2.00

Table 5
(continued)

Drug	*Pediatric dosing*	*Adult dosing*	*Formulation*	*Cost/day*
Trandolapril[R]	No data	Initial: 1 mg QD Max: 8 mg/day	T: 1 mg/2/4	$1.20
AT II receptor antagonists				
Candesartan	Initial: 0.13 mg/kg QD Max: 16 mg QD	Initial: 16 mg QD Max: 32 mg/day	T: 4 mg/8/16/32	$2.30
Eprosartan	No data	Initial: 600 mg QD Max: 800 mg/day	T: 400 mg/600	$3.24
Irbesartan	Initial: >6 y/o 75 mg QD Max: 150 mg/day	Initial: 150 mg QD Max: 300 mg/day	T: 75 mg/150/300	$2.36
Losartan	Initial: >6 y/o 0.7 mg/kg QD [>20 kg: 25 mg; >50 kg: 50 mg] Max: [>20 kg: 50 mg; >50 kg: 100 mg]	Initial: 50 mg QD Max: 100 mg/day	T: 25 mg/50/100	$2.37
Olmesartan	No data	Initial: 20 mg QD Max:: 40 mg QD	T: 5 mg/20/40	$2.38
Telmisartan	No data	Initial: 40 mg QD Max: 80 mg/day	T: 20 mg/40/80	$2.40
Valsartan	Initial: 1–2 mg/kg QD [40 mg/day] Max: 3.4 mg/kg [160 mg/day]	Initial: 80 mg QD Max: 320 mg/day	T: 40 mg/80/160/320 Extemp: 4 mg/ml	$2.60
Renin inhibitors				
Aliskiren	No data	Initial: 150 mg QD Max: 300 mg/day	T: 150 mg/300	$2.82

Table 5
(continued)

Drug	*Pediatric dosing*	*Adult dosing*	*Formulation*	*Cost/day*
Calcium channel blockers				
Amlodipine	Initial: 0.1–0.2 mg/kg QD [2.5–5 mg] Max: 0.6 mg/kg [10 mg]	Initial: 5 mg QD Max: 10 mg/day	T: 2.5 mg/5/10 Extemp: 1 mg/ml	$1.72
Diltiazem	*There are numerous formulations and dosing recommendations, please consult reference text*			
Felodipine	Initial: 2.5 mg QD Max: 10 mg/day	Initial: 5 mg QD Max: 10 mg/day	T(ER): 2.5 mg/5/10	$1.51
Isradipine	Initial: 0.15–0.2 mg/kg/day *Regular:* ÷BID/TID *CR:* ÷QD/BID	Initial: *Regular:* 2.5 mg BID *CR:* 5 mg QD Max: 20 mg/day	C: 2.5 mg/5 CR: 5 mg/10 Extemp: 1 mg/ml	*Regular*: $2.60 *CR*: $2.86
Nifedipine	0.25 mg/kg/dose Q 4–6 h	Not recommended in adults	C: 10 mg/20	
Nifedipine ER	Initial: 0.25 mg/kg ÷ QD/BID Max: Not established	Initial: 30 mg QD Max: 180 mg/day	T: 30 mg/60/90	$1.36
Nisoldipine	No data	Initial: 20 mg QD Max: 60 mg/day	T: 10 mg/20/30/40 [original formulation]	$2.55
Verapamil	*There are numerous formulations and dosing recommendations, please consult reference text*			

Table 5
(continued)

Drug	*Pediatric dosing*	*Adult dosing*	*Formulation*	*Cost/day*
Diuretics				
Amiloride[R]	Initial: 0.4–0.625 mg/kg QD Max: 20 mg	Initial: 5–10 mg QD Max: 20 mg	T: 5 mg	$1.25
Chlorothiazide[R]	Initial: 10–20 mg/kg ÷ QD/BID Max: <2 y/o 375 mg/day >2 y/o 1 g/day	Initial: 125–500 mg QD/BID Max: 2 g/day	T: 250 mg/500 Susp: 250 mg/5 ml	$0.25–0.50
Chlorthalidone[R]	Initial: 0.3 mg/kg QD/QOD Max: 2 mg/kg/day [50 mg/day]	Initial: 15 mg QD Max: 50 mg QD	T: 15 mg/ 25/50/100	$0.23
Hydrochlorothiazide	Initial: 1–2 mg/kg ÷ QD/BID Max: <2 y/o 37.5 mg/day >2 y/o 50 mg/day	Initial: 25 mg QD/BID Max: 100 mg/day	C: 12.5 mg T: 25 mg/50 Soln: 50 mg/5 ml	$0.09–0.18
Spironolactone[R]	Initial: 1 mg/kg ÷ QD/BID Max: 3 mg/kg/day—may need higher doses with mineralocorticoid excess	Initial: 25 mg QD/BID Max: 200 mg/day	T: 25 mg/50/100 Extemp: 5 mg/ml; 1 mg/ml	$0.46–0.92
Triamterene[R]	Initial: 1–2 mg/kg/day ÷BID Max: 3–4 mg/kg/day [300 mg]	Initial: 50–100 mg QD/BID Max: 300 mg/day	C: 50 mg/100	$1.29–2.58
Vasodilators				
Hydralazine[R]	Initial: 0.7–1 mg/kg ÷ BID/QID Max: 7.5 mg/kg/day [100 mg]	Initial: 10 mg QID Max: 300 mg/day	T: 10 mg/25/50/100 Extemp: 20 mg/5 ml	$1.64

Table 5
(continued)

Drug	*Pediatric dosing*	*Adult dosing*	*Formulation*	*Cost/day*
Minoxidil[R]	Initial: 0.1–0.2 mg/kg ÷ QD/BID [5 mg] Max: 50 mg/day	Initial: 2.5–5 mg QD Max: 100 mg/day	T: 2.5 mg/10 Extemp: 2 mg/ml	$0.85
β-Adrenergic antagonists				
Acebutolol[R] (ISA)	No data	Initial: 400–800 mg QD Max: 1200 mg/day	C: 200 mg/400	$1.34
Atenolol[R] (B1-selective)	Initial: 0.5–1 mg/kg QD Max: 2 mg/kg/day [100]	Initial: 25–50 mg QD Max: 100 mg/day	T: 25 mg/50/100 Extemp: 2 mg/ml	$0.85
Bisoprolol[R] (B1-selective)	No data	Initial: 5 mg QD Max: 20 mg/day	T: 5 mg/10	$1.23
Metoprolol ER	Initial: 1 mg/kg QD [50 mg] Max: 2 mg/kg [100 mg]	Initial: 50–100 mg QD Max: 400 mg/day	T(ER): 25 mg/50/100/200 Extemp: 10 mg/ml	$0.90
Nadolol[R]	No data	Initial: 40–80 mg QD Max: 640 mg/day	T: 20 mg/40/80/120/160	$1.05
Propranolol	Initial: 0.5–1 mg/kg ÷ BID/TID Max: 16 mg/kg/day	Initial: 40 mg BID LA: 80 mg QD Max: 640 mg/day	T: 10 mg/20/40/60/80 LA: 60 mg/80/120/160 Extemp: 1 mg/ml	$1.38 *CR:* $2.40
Timolol	No data	Initial: 10 mg BID Max: 60 mg/day	T: 5 mg/10/20	$1.00
Labetalol (α- and β-)	Initial: 1–3 mg/kg/day ÷ BID Max: 10–20 mg/kg [1200 mg]	Initial: 100 mg BID Max: 2.4 g/day	T: 100 mg/200/300 Extemp: 10 mg/ml	$1.00
Carvedilol (α- and β-)	No data	Initial: 6.25 mg BID Max: 50 mg/day	T: 3.125 mg/6.25/12.5/25 C(ER): 10 mg/20/40/80	$4.20 ER: $4.54

Table 5
(continued)

Drug	*Pediatric dosing*	*Adult dosing*	*Formulation*	*Cost/day*
Central α-adrenergic agonists				
Clonidine	Initial: <12 y/o: 5–10 mcg/kg ÷ BID/TID >12 y/o: 0.2 mg/kg ÷ BID/TID Max: Not established	Initial: 0.1 mg BID Max: 2.4 mg/day	T: 0.1 mg/0.2/0.3 Transdermal: 0.1 mg/0.2/0.3	$0.50 TD:$4.26
Guanfacine[R]	Max: 0.9 mg/day No data	Initial: 1 mg QD Max: 2 mg/day	T: 1 mg/2	$0.71
α-adrenergic antagonists				
Doxazosin	Initial: 1 mg QD Max: 4 mg/day	Initial: 1 mg QD Max: 16 mg/day	T: 1 mg/2/4/8	0.92
Prazosin	Initial: 0.05–0.1 mg/kg ÷ BID/TID Max: 0.5 mg/kg/day	Initial: 1 mg BID/TID Max: 20 mg/day	C: 1 mg/2/5	$0.64–0.96
Terazosin	No data	Initial: 1 mg QD Max: 20 mg/day	C: 1 mg/2/5/10	$1.60

R: dosing adjustments/concerns with renal dysfunction.
Cost/day: based on average AWP using initial adult dosing recommendations.

inhibitors, and the dosage should be significantly lower than the dosage recommended for older children *(35,36)* (see Chapter 21).

Captopril has a beneficial blood pressure-lowering effect in children with renal parenchymal and renovascular disease *(26,28–31)*; however, the increased incidence of cough and need for more frequent dosing have led to greater use of the newer, longer acting ACE inhibitors (e.g., enalapril, lisinopril). Once-daily dosing with enalapril or lisinopril lowers trough blood pressure in a dose-dependent manner in children with hypertension *(32,33)*. In these prospective studies, the lowest dosage group (0.02 mg/kg) did not have a consistent blood pressure-lowering response, and the initial recommended dosage for both agents is 0.08 mg/kg given once daily. In a fairly large study from a pediatric perspective, the effectiveness, safety, and dose–response relationship of fosinopril were studied in 253 children with high or high-normal blood pressure *(37)*. Treatment with fosinopril significantly lowered systolic and diastolic blood pressure during the 4-week study. Because there was no apparent dose–response relationship the initial recommended dose for children is 0.1 mg/kg given once daily; however, a post hoc analysis suggested that black children may require higher doses to produce similar blood pressure-lowering effects *(38)*. If a child is receiving a moderate dose of an ACE inhibitor and the blood pressure-lowering effect diminishes toward the end of the dosing interval (e.g., trough BP) twice-daily dosing should be considered prior to adding a second antihypertensive drug. The pharmacokinetic parameters of enalapril and quinapril in hypertensive children are similar to those reported for adults *(39,40)*.

The most common adverse effects reported in children receiving ACE inhibitors include cough, hypotension, and deterioration of renal function *(41,42)*. The decline in renal function and hypotension is noted most in neonates or children with preexisting renal disease or volume depletion and is uncommon in the well-hydrated child with normal renal function. Less common adverse effects include angioedema, hyperkalemia, rash, anemia, and leukopenia *(43)*.

The use of ACE inhibitors during pregnancy has been associated with fetal and neonatal toxicity. ACE inhibitor fetopathy is typically associated with ACE inhibitor exposure during the second and third trimesters of pregnancy and characterized by fetal hypotension, anuria-oliogohydramnios, growth restriction, pulmonary hypoplasia, renal tubular dysplasia, and hypocalvaria *(44)*. More recently, ACE inhibitor exposure during the first trimester has been associated with an increased risk of birth defects, namely cardiovascular abnormalities *(45)*. Because of the potential adverse fetal and neonatal effects, ACE inhibitors should probably not be used as the initial treatment for hypertension in this population unless the expected benefit clearly exceeds the potential risk such as might be the situation in adolescent girls with CKD, DM, or difficult to control/resistant hypertension. Adolescents of childbearing potential that are prescribed ACE inhibitors are to be informed of the potential risks of ACE inhibitors on the developing fetus and counseled on proper birth control measures. ACE inhibitors are contraindicated in children with a history of angioedema and should be used with great caution in children with bilateral renal artery stenosis or renal artery stenosis in a solitary kidney.

ANGIOTENSIN II (AT II) RECEPTOR ANTAGONISTS

AT II receptor antagonists block the binding of angiotensin II to the angiotensin receptor (type 1) located in vascular smooth muscle and the adrenal gland. AT II receptor antagonists

prevent the pressor effect of angiotensin II and inhibit angiotensin II-stimulated aldosterone secretion from the adrenal gland.

Similar to ACE inhibitors, AT II receptor antagonists appear to be well tolerated and effectively lower blood pressure in hypertensive children as monotherapy or delivered with other antihypertensive agents *(46–50)*. The pharmacokinetic profile of valsartan and irbesartan in children is similar to that observed in adult patients with hypertension. Once-daily candesartan effectively reduced clinic and 24-h ambulatory blood pressure in 11 children studied by Franks et al. *(46)*. Similarly, valsartan effectively lowered blood pressure in a group of 88 children less than 5 years of age with untreated or inadequately treated hypertension *(50)*. As would be expected, the majority of these young children had an underlying urologic or kidney disease associated with hypertension. Finally, although primarily a pharmacokinetic study, Sakarcan et al. *(47)* detected a BP-lowering effect in a group of children receiving irbesartan.

There are relatively few reports of adverse effect of AT II receptor antagonist in the pediatric studies with an adverse effect profile similar to placebo. The most commonly reported adverse events in the pediatric studies were concurrent infectious illnesses which are common in this population. Other reported events include hyperkalemia, headache, and rare events of pruritus, malaise, hepatitis, decreased appetite, and blurred vision. Due to the fetal and neonatal toxicity noted with drugs that act on the renin–angiotensin system *(44,45)*, AT II receptor antagonist should not be given during pregnancy, and their use in adolescents of childbearing potential should be undertaken with caution as described in the preceding section on ACE inhibitors. If prescribed, adolescents of childbearing potential are to be informed of the potential risks and counseled on proper birth control measures.

RENIN INHIBITORS

Renin inhibitors block the circulating enzyme renin that catalyzes the conversion of the substrate angiotensinogen to the inactive peptide angiotensin I. Angiotensin I is converted to the active peptide angiotensin II, which in turn influences blood pressure by direct vasoconstriction of the arterial vasculature, increased sympathetic nervous system activity, direct cardiovascular inotropic effect, and aldosterone-enhanced salt and water retention.

Studies of direct renin inhibitors in children are currently in progress, and no data are presently available on their effectiveness or safety in the pediatric population. Aliskiren, the only direct renin inhibitor currently available, effectively lowers systolic and diastolic BP in adults *(51)*. The most common adverse effect associated with higher does of aliskiren was diarrhea.

CALCIUM CHANNEL BLOCKERS (CCBS)

The contraction of cardiac and vascular smooth muscle and peripheral vascular resistance are dependent on the inward flux of calcium. Dihydropyridine calcium channel blockers (CCBs) such as amlodipine, felodipine, isradipine, nicardipine, nifedipine, and nisoldipine inhibit the inward movement of calcium and cause relaxation of the arterial vasculature and decreased peripheral vascular resistance. In contrast to non-dihydropyridine CCBs such as verapamil and diltiazem, dihydropyridine CCBs have a negligible effect on cardiac conduction and contractility.

CCBs effectively lower blood pressure in hypertensive children and are well tolerated *(52,53)*. Amlodipine lowered the systolic and diastolic blood pressure of hypertensive chil-

dren in a dose-dependent manner when administered once daily *(54)*. Amlodipine is ideally suited for the treatment of childhood hypertension because the prolonged elimination half-life (e.g., >30 h) permits once-daily dosing and the physicochemical properties allow the drug to be compounded as a liquid suspension (extemporaneous formulation) that permits treatment of children unable to swallow tablets/capsules and allows dose titration in small increments. In children able to swallow a tablet or capsule formulation, sustained release of nifedipine appears to be well tolerated.

The most common adverse effects reported in children receiving CCBs include flushing, headache, peripheral edema, and fatigue *(55–57)*. Other reported adverse effects include gingival hyperplasia, chest pain, and nausea and vomiting *(43)*.

The use of short-acting nifedipine or other short-acting CCBs in children with hypertension is not recommended for long-term therapy, and their use to control acute elevations of blood pressure is controversial *(58–61)*. Short-acting nifedipine in adult patients is associated with an increased risk of adverse cardiac and neurologic events *(21,62)*. In general, short-acting nifedipine appears to be effective in children with acute blood pressure elevation *(58)*; however, profound and unpredictable drops in blood pressure have been observed in children receiving short-acting nifedipine, occasionally resulting in catastrophic CNS events *(63)*. When used, the initial nifedipine dosage should be 0.1–0.25 mg/kg and should be avoided in children with an underlying acute CNS injury *(58,64)*.

DIURETICS

Thiazide diuretics are the most common and effective diuretics prescribed for hypertension. Loop diuretics are not useful as long-term antihypertensive agents due to the adaptive processes that limit their effectiveness *(65)* but may be effective as adjuvant therapy in volume-overloaded patients that are resistant to the effects of thiazide diuretics, such as patients with chronic renal failure. The potassium-sparing diuretics (e.g., spironolactone and amiloride) are specifically indicated for hypertension due to mineralocorticoid excess and to diminish thiazide and loop diuretic-induced hypokalemia.

The initial blood pressure-lowering effect of thiazide diuretics results from an increased urinary loss of sodium and extracellular fluid volume contraction. With chronic dosing, sodium balance and extracellular fluid volume return toward normal; however, the lower blood pressure is maintained by a decline in peripheral vascular resistance. The mechanism(s) responsible for the changes in vascular resistance are unclear. The antihypertensive response to thiazide diuretics is dependent on sodium intake, and a high-sodium intake will attenuate the antihypertensive effect and is a common cause of apparent resistance to therapy (Table 5).

Thiazide diuretics, alone or in combination with β-adrenergic antagonists, lower blood pressure in children with hypertension *(18,66)*. In a placebo-controlled trial examining the blood pressure-lowering effect of the combination drug bisoprolol/hydrochlorothiazide, systolic and diastolic blood pressures were significantly reduced as compared to a group of children randomized to placebo *(18)*.

The thiazide dose–antihypertensive response relationship in adults is relatively flat, such that there is little further blood pressure lowering but increased incidence of adverse effects with larger doses. Common adverse effects with diuretics are hypokalemia, hyponatremia, alkalosis, and extracellular fluid volume depletion. Caution is suggested when adding an ACE inhibitor to a child receiving diuretics as the diuretic-induced volume depletion may increase the risk of hypotension and renal dysfunction. Ototoxicity is a reported side effect

of loop diuretics, and the risk increases with high doses, kidney failure, and concomitant use of other ototoxic drugs such as aminoglycosides.

β-ADRENERGIC RECEPTOR ANTAGONISTS

β-Adrenergic receptor antagonists decrease blood pressure through several mechanisms including decreased cardiac output, decreased secretion of renin and aldosterone, altered central nervous system sympathetic activity, and potentiation of natriuretic peptides.

Cardioselective β-adrenergic receptor antagonists such as acebutolol, atenolol, bisoprolol, and metoprolol have a greater affinity for the $beta_1$-adrenergic receptor, whereas nonselective drugs such as carvedilol, labetalol, nadolol, propranolol, and timolol interact with both $beta_1$- and $beta_2$-adrenergic receptors. The preferential effect of cardioselective drugs for $beta_1$-adrenergic receptors is relative, and at higher doses, cardioselective drugs will inhibit the $beta_2$-adrenergic receptors that are located in bronchial musculature. The clinical importance of intrinsic sympathetic activity is not well defined. Carvedilol and labetalol are nonselective beta-adrenergic receptor antagonists that also have peripheral $alpha_1$-adrenergic blocking activity.

Beta-adrenergic receptor antagonists lower blood pressure in hypertensive children when used alone or in combination with other antihypertensive agents *(18,66–68)*. Great interindividual variation exists in the amount of propranolol needed to lower blood pressure as propranolol is metabolized by the liver prior to entering the systemic circulation (e.g., first-pass effect). This results in unpredictable plasma concentrations following oral administration and a wide range of effective dosages. The combination drug bisoprolol and hydrochlorothiazide lowered systolic and diastolic blood pressure in children with hypertension *(18)*. Metoprolol, a cardioselective agent, effectively lowered blood pressure in a group of hypertensive adolescents *(69)*.

The most common adverse effects from beta-adrenergic receptor antagonists are related to the central nervous system and include dizziness, light-headedness, fatigue, depression, and hallucinations. Other adverse effects are bradycardia, postural hypotension, cold extremities, and nausea. Beta-adrenergic receptor antagonists can mask the premonitory signs associated with hypoglycemia in diabetic patients and should not be used in patients with bronchospastic disease.

CENTRALLY ACTING SYMPATHOLYTIC AGENTS

Stimulation of the $alpha_2$-adrenergic receptors in the central nervous system decreases sympathetic outflow. Centrally acting agents such as clonidine and guanabenz are commonly reserved for hypertension recalcitrant to multiple antihypertensive drugs. Clonidine may be the preferred antihypertensive agent in children receiving pharmacologic treatment of a hyperactivity disorder. The reported experience with centrally acting agents is limited to adolescents with essential hypertension *(70–72)*.

Side effects are common with the use of centrally acting agents. Dry mouth, sedation, fatigue, dizziness, weakness, and constipation are typically dose related and tend to decrease with continued dosing. Discontinuation of centrally acting agents should be gradual as abrupt withdrawal can result in symptoms such as agitation, headache, tremor, and hypertension.

PERIPHERAL ADRENERGIC ANTAGONIST

Alpha$_1$-adrenergic receptor antagonist such as doxazosin, prazosin, and terazosin blocks the pressor effect of adrenergic stimulation on the vasculature resulting in reduced arteriolar resistance and venous capacitance. Alpha$_1$-adrenergic receptor antagonists are usually reserved for severe or drug-resistant hypertension and are infrequently prescribed in children. The alpha$_1$-adrenergic receptor antagonists can be considered for initial therapy in children with the insulin-resistant syndrome, a syndrome characterized by obesity, insulin resistance, lipid abnormalities, and hypertension, as the syndrome is associated with sympathetic overactivity *(73)*, and alpha$_1$-adrenergic receptor antagonists have positive effect on the lipid profile.

The first-dose phenomenon, a marked postural hypotensive response that occurs shortly after the initial dose or with a dosage increase, is common and more likely to occur in patients receiving diuretics or beta-adrenergic receptor antagonists. The most common adverse effects associated with alpha$_1$-adrenergic receptor antagonists are dizziness, headache, fatigue, palpitations, and nausea.

VASODILATORS

Vasodilators such as hydralazine and minoxidil produce arteriolar vasodilation through a direct action on vascular smooth muscle. Minoxidil successfully lowers blood pressure in children *(74,75)* but is best reserved for severe and drug-resistant forms of hypertension.

The predominant side effects of vasodilators are fluid and salt retention and cardiac stimulation. Cardiac output is increased by enhanced venous return and sympathetic activity. Patients with poorly compliant ventricles, such as patients with severe left ventricular hypertrophy and diastolic dysfunction, may develop heart failure when prescribed vasodilators. Concomitant treatment with diuretics or beta-adrenergic receptor antagonist may modify the fluid retention and cardiac stimulation. Flushing, headache, palpitations, hypotension, and palpitation are commonly observed with vasodilators. Growth of hair on the face, back, arms, and legs occurs in all patients receiving minoxidil and can be very distressing for young girls. Hydralazine can cause a drug-induced lupus syndrome.

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32 Management of Hypertensive Emergencies

Craig W. Belsha, MD

Contents

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.

DEFINITIONS OF HYPERTENSIVE CRISES, EMERGENCIES, AND URGENCIES

Hypertension in childhood is classified by The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents into two

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_32
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Table 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

SBP, systolic blood pressure, DBP, diastolic blood pressure.
Adapted from *(1,4)*.

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. 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 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 *(2)*. 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 *(3)*.

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 mmHg in adults to constitute a "hypertensive crisis" *(4,5)*. 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 *(5,6)*. 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 *(5,6)*.

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 *(5,6)*. 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 *(7)*. 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 *(8,9)*.

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 1963, 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) *(10)*. Neurologic complications (facial palsy, convulsions, cerebrovascular lesions) were present in one-third 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 2). Fortunately, long-term outcome was improved with only 4% experiencing sustained neurologic damage *(11)*. 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 *(12)*. Eighteen of 27 (66%) had left ventricular hypertrophy by ECG, 16 of 27 (60%) had retinal vascular lesions, and 3 of 27 (11%) had renal failure.

Table 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%

BP, blood pressure.
Adapted from *(11)*.

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 *(13,14)*. Older case series have reported renal problems as the cause of hypertensive emergencies or urgencies in children in over 80% of patients *(11)*. A more recent series of children treated with an intravenous antihypertensive agent reported that 55% had associated renal disease *(15)*.

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 *(16)*. In neonates, renovascular disease secondary to an aortic or renal thrombus related to an umbilical artery catheter is a common cause of a hypertensive emergency as well as congenital renal anomalies and coarctation of the aorta. Outside of the newborn period, children may have renal parenchymal disease such as glomerulonephritis or reflux nephropathy or renovascular disease or endocrine disease. In adolescents, renal parenchymal diseases may also be seen, but additional causes of severe hypertension may include pre-eclampsia and drug intoxication (cocaine, amphetamines). While most adults presenting to the emergency department with severe hypertension have a known diagnosis of hypertension (80%) *(17)*, 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 *(18,19)*. Abrupt withdrawal of either a beta-blocker or clonidine may result in "rebound" hypertension that may require urgent intervention *(20)*.

PATHOPHYSIOLOGY

One of the key homeostatic mechanisms to prevent organ injury is autoregulation. While present in many tissues, autoregulation of cerebral blood flow is the most well studied *(21,22)*. 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 *(23)*. In adults, autoregulation appears to be present over the mean arterial pressure range from 60 to 150 mmHg *(24)*. Autoregulation appears early in development and is present in later fetal and neonatal lambs and neonatal dogs and humans *(25,26)*. 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 *(25)*. The autoregulatory plateau appears to be more narrow 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 *(25)*.

In adults with uncontrolled chronic hypertension, there is a shift in the autoregulatory curve, providing constant cerebral blood flow at higher mean arterial pressures *(24)*. 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 *(27–29)*, the effects of chronic hypertension on developmental differences in cerebral autoregulation during childhood and adolescence remain unknown.

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 *(30)*. This impairment in autoregulation has been demonstrated in severely hypertensive adults *(31)*, and studies have demonstrated differential effects of antihypertensive agents on cerebral blood flow during blood pressure reduction *(32)*. 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 *(33,34)*. Inhibition of δ(delta)PKC led to stability of the BBB in a hypertensive rat model, suggesting this may be a therapeutic target for prevention of BBB disruption in this condition.

The mechanisms of hypertension leading to development of hypertensive emergencies often involve the renin–angiotensin–aldosterone system *(9,35–37)*. These have been reviewed in detail elsewhere *(38)*. 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-Kβ(beta). 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 and medications *(39)*.

CLINICAL PRESENTATION

Children with severe hypertension may present with major symptoms or be asymptomatic *(3)*. After confirming that blood pressure has been measured with the proper size cuff and technique, the initial history and physical exam should focus on symptoms and signs of end-organ damage *(40,41)*. 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 *(42,43)*. Facial nerve palsy has also been a CNS finding in children with a hypertensive emergency *(44–47)*. Hemorrhages or exudates and papilledema are frequently reported on fundoscopic exam *(48–50)*. 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. Exopthalmos may be associated with hyperthyroidism and an abdominal mass may be seen with Wilm's tumor, polycystic kidney disease, neuroblastoma, or congenital renal anomalies *(51,52)*. Skin lesions such as café-au-lait spots and axillary freckling may suggest neurofibromatosis which may be associated with renovascular hypertension or pheochromocytoma *(53)*. Diminished femoral pulses or reduced blood pressure in the legs suggest coarctation of the aorta *(40)*. 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 *(35)*.

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 *(54)*. Adolescent girls should have a pregnancy test as pre-eclampsia may present with severely elevated blood pressure *(55)*. 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 *(56,57)*. If signs of encephalopathy are present, a computed tomography study of the head should be obtained to evaluate 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) *(58–63)*. 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 *(57,64,65)*.

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 a hypertensive urgency. 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 *(35)*.

A number of antihypertensive medications are available with established efficacy *(66)*. Unfortunately, few have undergone rigorous testing in children and less than half of current IV antihypertensive agents marketed in the USA have pediatric labeling *(9)*. 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. Meta-analysis of adult studies also fails to prove beneficial effects of treatment on morbidity and mortality *(67)*. Most of these trials, however, involved small numbers of patients with differing definitions for enrollment and outcome, treatment regimens, and length of follow-up

(68). 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 *(1,4)*. 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. About 23% 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 *(11)*.

The goal for 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)*. 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. The Fourth Report on the Diagnosis, Evaluation, and 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)*. 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 antihypertensives depending on the child's symptomatology.

Intravenous antihypertensives which have proven most useful in treating severe hypertension include nicardipine, labetolol, sodium nitroprusside, and hydralazine. Additional intravenous agents which may be occasionally useful include esmolol, fenoldopam, and possibly enalaprilat. 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 3.

Diazoxide, an intravenous direct vasodilator used frequently in the past by bolus injection *(69–71)*, 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 *(9,72)*. Use of short-acting nifedipine has been abandoned in adults *(73)* 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 with in-hospital use *(74–76)*, 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 *(77–82)*. 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 treatment of hypertension *(1)*.

Sodium nitroprusside, a direct vasodilator of arteriolar and venous smooth muscle cells, has been used for treatment of severe hypertension in childhood since the 1970s *(83,84)*. 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 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 *(85)*. Toxicity occurs as a result of the metabolism of nitroprusside

Table 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/min	IV infusion	Very short-acting; constant infusion. May cause bradycardia
Hydralazine[a]	Vasodilator	0.2–0.6 mg/kg/dose	IV bolus or IM	Causes reflex tachycardia, headaches, fluid retention
Labetolol	α(alpha)- and β(beta)-blocker	Bolus: 0.2–1 mg/kg/dose up to 40 mg/dose Infusion: 0.25–3 mg/kg/h	IV infusion or bolus	Use with caution in asthma, heart failure. Preferred in neurologic emergency
Nicardipine	Calcium channel blocker	1–2 μg/kg/min	IV infusion	May cause reflex tachycardia. Preferred in neurologic emergency
Sodium nitroprusside	Vasodilator	0.53–10 μg/kg/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/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/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/dose	po	Stable suspension can be compounded
Minoxidil	Vasodilator	0.1–0.2 mg/kg/dose	po	Most potent oral vasodilator, long-acting

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.
Adapted from *(1)*.

to cyanide and thiocyanate. Toxic accumulation of cyanide leads to development of metabolic acidosis with elevated lactate levels, tachycardia, altered consciousness, dilated pupils, and methemoglobinemia. Cyanide levels (toxic > 2 μg/mL) should be monitored in the setting of hepatic dysfunction *(86)*. Thiocyanate toxicity is suggested by symptoms of altered mental status, nausea, seizures, skin rash, psychosis, anorexia, or coma *(72)*. Thiocyanate levels should be monitored daily if used for >48 h, with dosages above 4 μg/kg/min or with renal dysfunction. Levels should be less than 50 mg/L. 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 *(72)*, which may lessen the risk of toxicity. Most authorities recommend limiting nitroprusside use to situations where no other suitable agents are available or to brief periods of time *(6,9)*.

Labetolol 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 *(87)*. 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 *(87)*. The medication is metabolized by the liver and elimination is not altered by renal dysfunction. Labetolol is 3–7 times more potent as a β-blocker than α(alpha)-blocker *(87)*. The beta effects may lead to bronchospasm and bradycardia and use of labetolol 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 *(88,89)*. As compared with sodium nitroprusside, systemic and cerebral vascular resistance are decreased proportionally, maintaining cerebral blood flow to a greater extent with labetolol *(32)*. Case series in children have demonstrated its usefulness in the pediatric population *(11,90)*. 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/h with a maximum 24 h dose of 300 mg *(1,6)*.

Nicardipine, a second-generation dihydropyridine calcium channel blocker, has greater selectivity for vascular smooth muscle than cardiac myocytes. It has strong cerebral and coronary vasodilatory activity and minimal inotropic cardiac effects leading to favorable effects on myocardial oxygen balance *(91)*. Efficacy in reducing blood pressure was similar to IV sodium nitroprusside in adults. 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 labetolol, it is recommended for hypertension management in neurologic emergencies such as hypertensive encephalopathy as it does not increase intracranial pressure *(88,89)*.

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 *(92–98)*. It has proven to be safe and is generally well tolerated. The recommended pediatric dosage is 1–3 μg/kg/min *(1)*. Like most other agents, it has not been evaluated by clinical trials in the pediatric population. A multicenter trial was recently terminated when the drug was sold by the sponsor of the trial. 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 *(99)*. Phlebitis has been reported at the site of administration with higher dosage concentrations *(95)*, suggesting the medication should in this situation be given through a central line.

Hydralazine is a direct vasodilator of arteriolar smooth muscle. The mechanism of action is unclear, although it may involve alterations in intracellular calcium metabolism *(85)*. 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 *(72)*. Average maximum decrease in blood pressure occurs 10–80 min after intravenous administration *(9)*. This medication can be given intramuscularly. The recommended dosage for pediatric patients is 0.1–0.6 mg/kg/dose given intravenously every 4–6 h *(1,86)*. Given as a bolus rather than continuous intravenous medication, hydralazine may be more useful in an individual with a hypertensive urgency that is 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 labetolol or nicardipine has been prepared by the hospital pharmacy.

Esmolol is an ultrashort-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 *(100,101)*. 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/min by group and no serious adverse events occurred *(101)*. 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 pressuring 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 *(6,102)*. It has also been used as a renal protective drug in critically ill adult and pediatric patients *(102,103)*. One pediatric trial conducted in 77 children aged 1 month to 12 years undergoing controlled hypotension during surgery compared response to one of the four doses of fenoldopam (0.05, 0.2, 0.8, or 3.2 μg/kg/min) *(104)*. Dosages of 0.8 and 3.2 μg/kg/min significantly decreased blood pressure but resulted in increases in heart rate of 9–17 beats/min. 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 use of this agent for a hypertensive emergency in childhood has been reported *(105)*.

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 is 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 *(6)*. One pediatric case series in ten 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 enalaprilate administration that persisted generally

for a median of 12 h *(106)*. 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 recently 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 *(107)*. 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 *(108)*. Pediatric studies with this agent are expected in the near future.

Clonidine is a centrally acting $\alpha(\text{alpha})_2$-adrenergic agonist which decreases cerebral sympathetic outflow. Its onset of action is 30–60 min after administration and duration is 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 *(20)*. 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 *(109)*. 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 is limited to chronic oral or transdermal therapy in adolescents *(110,111)*, 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 *(112)*. Onset of action is by 1 h with peak effect at 2–3 h when administered orally *(113)*. Medication half-life is 3–8 h. A stable extemporaneous suspension of isradipine may be compounded for use in small children *(114)*. Several pediatric series of the use of this medication for management of hypertension have been reported *(115–117)*. Isradipine given sublingually to 27 adults with severe hypertension demonstrated a reduction of mean arterial pressure of 22% by 2 h *(118)*. A recent report in 218 children with acute hypertension receiving isradipine at a mean dosage of 0.08 mg/kg (0.02–0.22 mg/kg) demonstrated a median decrease in systolic BP of 15.7% and diastolic BP of 23.4%. The greatest decrease in BP was observed in children below age 2 years. Higher dosages were associated with more frequent drop in mean arterial pressure >25%. The most common adverse events included vomiting, nausea, and headache *(119)*.

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 *(85)*. Reported use in childhood includes severe chronic hypertension refractory to other medications and for acute BP elevations in children with chronic hypertension *(120,121)*.

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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33 Pediatric Antihypertensive Clinical Trials

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Contents

INTRODUCTION

Historically, systemic hypertension was felt to occur in 1–4% of children *(1–5)*; however, the prevalence is now increasing because of the influence of childhood obesity *(6,7)*. Over the past three decades, childhood obesity has increased dramatically and has been deemed an epidemic by the Centers for Disease Control and Prevention *(8)*. The 2002 National Health and Nutrition Examination Survey reported that the prevalence of overweight and obese children aged 6–19 years was 31%, a 45% increase from the previous survey *(9)*. Not only is the prevalence of pediatric hypertension increasing, but also the condition is frequently underdiagnosed *(10,11)*. In younger children, hypertension is often secondary to an underlying disorder while primary (or essential) hypertension accounts for up to 95% of cases in adolescents *(12,13)*. Hypertension in this age group is linked to obesity and risk factors associated with metabolic syndrome that can lead to cardiovascular disease in later life, including lipid abnormalities and insulin resistance. Obesity has been linked to comorbid conditions in children, including type 2 diabetes mellitus, hypertension, and hyperlipidemia *(14,15)*.

There is major concern that the increasing prevalence of these cardiovascular risk factors in children will lead to a dramatic rise in adult cardiovascular disease and neurologic

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From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9_33
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events. The presence of obesity, type 2 diabetes, hyperlipidemia, and hypertension in childhood has been linked to elevated left ventricular mass and carotid intima-media thickness, as well as peripheral endothelial dysfunction *(15–18)*. The presence and severity of coronary atherosclerotic plaque in asymptomatic young adults are related to the number of risk factors present, including higher body mass index, hypertension, and hyperlipidemia *(19)*. A Danish study of 275,835 adults found that childhood body mass index was significantly associated with coronary artery events in adulthood *(20)*.

Given these trends, the number of children prescribed antihypertensive medications is likely to increase in coming years. Therapy for this condition is hampered, however, by uncertainty over the efficacy and safety of antihypertensive medicines in children. Agents that have been extensively tested and that have a long history of use in adults are often not supported by adequate data obtained in children; drug treatment of hypertension therefore presents a challenge for the pediatrician.

In response to the small number of clinical drug trials in children, 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 pharmaceutical company that responds to a Food and Drug Administration (FDA)—issued written request for studies of their drug in pediatric patients *(21,22)*. The program was extended in January 2002 when Congress passed the Best Pharmaceuticals for Children Act and was subsequently renewed in September 2007. This program has been very successful in stimulating drug studies in children, and, as a result of the program, >200 drug labeling changes have been enacted for children *(22–24)*. The European Medicines Agency (EMEA) has recently started to require drug studies in children and has begun to receive pediatric investigation plans (PIPS) for new molecular entities, including antihypertensive products. Also, under the European Union Pediatric Regulation for already authorized and patented medicinal products, a PIP is required if a sponsor wants to apply for a variation of an existing marketing authorization (e.g., to add a new indication [including pediatric], a new pharmaceutical form, or a new route of administration). For off-patent medicines developed specifically for pediatric use and with an appropriate formulation, a new marketing authorization—the pediatric-use marketing authorization (PUMA)—can be obtained.

Approximately half of the products studied for US pediatric exclusivity have been found to have substantive differences in dosing, safety, or efficacy in children when compared with adult populations *(25)*. Twenty-nine of 131 drugs examined were found to be ineffective when studied in children. Several products that did not demonstrate efficacy (or for which a statistically significant dose response was not observed) were oral antihypertensive agents known to be effective in adults.

This chapter will present an overview of the pediatric antihypertensive studies done to date and will focus on the clinical trial design and factors associated with success or failure of the clinical trials.

PEDIATRIC ANTIHYPERTENSIVE CLINICAL TRIAL DESIGN

The FDA allows for several types of trial designs in the written request for an antihypertensive agent. The written request, issued by FDA before initiation of pediatric exclusivity studies, contains the required elements of the requested studies, including indication, number of studies, age ranges, trial design, sample sizes, and need for a pediatric formulation *(25)*. In the written requests for antihypertensive drugs, the FDA allows for four efficacy trial designs (Fig. 1) *(26)*. Of note, it is not necessary for the dose-ranging study to show that a certain drug is effective in treating pediatric hypertension in order for

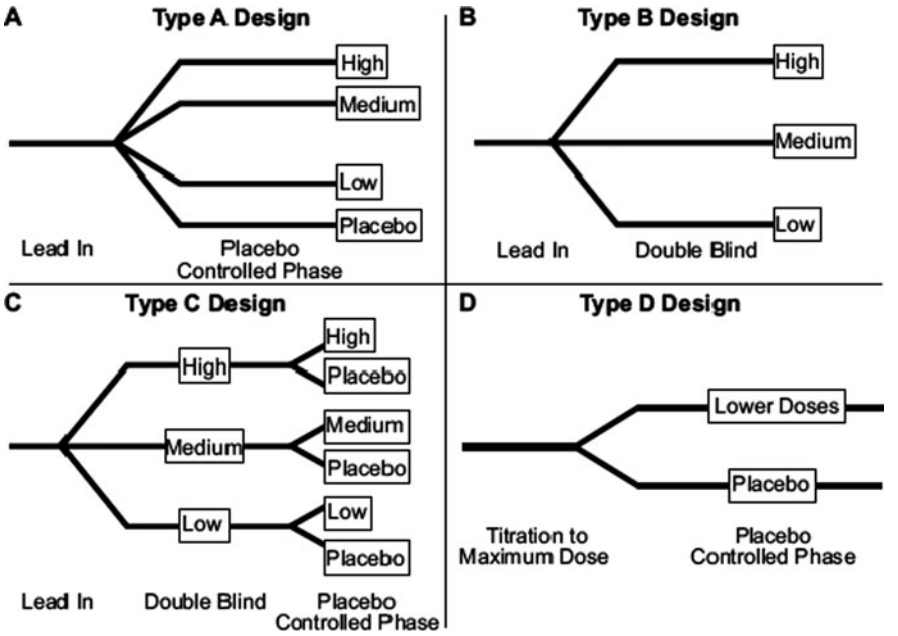

Fig. 1. During the double-blind phase, all of the patients received drug. A, Type A trial design; B, Type B trial design; C, Type C trial design; D, Type D trial design.

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. In other words, the study should show that the drug is either effective or ineffective. Thus, a trial not eligible for exclusivity is one that does not show a clear result; not one that shows a medication to be ineffective. Conducting these trials is further complicated by ethical and methodological issues unique to pediatric research *(27,28)*, in addition to compliance with the formal guidelines.

Trial Design A

In trial design A, patients are randomized to placebo or one of a few different dosages of the test medication (Fig. 1). It is recommended that the dosages be chosen to provide exposure in a range from slightly less than those achieved by the lowest approved adult dosage to slightly more than those achieved by the highest approved adult dosage. After a few 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 drug is considered ineffective. The major advantage of this trial type is its straightforward design and analysis. Both successful and unsuccessful trials are considered to be interpretable and therefore responsive to the written request.

However, the placebo-controlled design can lead to slow recruitment because parents are often uncomfortable with the possibility that their child may be placed on placebo. These trials can employ a 3:1 randomization scheme (thereby 3 times as many children receive active product) but some parents still have significant concerns about their child's partici-

pation, especially if the trial drug is available off-label. The knowledge that one could use a 3:1 randomization scheme was not evident in the early days of pediatric antihypertensive trials and thus this option was not frequently chosen by companies. In addition, some institutional review boards (IRBs) question the ethics of conducting placebo-controlled trials in children in general, in part due to the potential risk of adverse events while not on active therapy *(27,28)*. 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 drug. Therefore, despite the theoretic concerns over use of placebo *(27)*, short-term exposure to placebo in pediatric trials of antihypertensive medications appears to be safe *(29)*.

Trial Design B

To avoid the issues associated with a placebo-controlled trial, trial design B involves randomization to one of three dosages of the test medication as in trial A, but without a placebo arm (Fig. 1). If analysis of trial design 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 uninterpretable. Thus, a negative trial would be unresponsive to the written request. This trial has the simplest design of the four and avoids the aforementioned 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. Finally, the lack of controls does not allow adequate assessment of safety.

Trial Design C

Trial design C employs a more complex design in order to avoid use of a true placebo arm as in trial design B, while adding the ability to obtain interpretable results regardless of the outcome of the trial, as in trial A (Fig. 1). Trial design C begins like trial design B with randomization to one of a few dosages of the study drug. In addition, it includes a randomized withdrawal phase. At the end of the treatment period, patients are rerandomized 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 design 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, or that the drug was ineffective. Thus, as in trial design A, the trial would be considered interpretable regardless of the outcome, and therefore, responsive to the written request. Having two chances to meet eligibility for exclusivity is a major advantage of this trial design. In addition, minimizing the use of an explicit placebo arm likely makes this type of trial more appealing when presented to parents and IRBs.

Trial Design D

In trial design D, the entire trial is built around randomized drug withdrawal (Fig. 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 design C, trial design D minimizes the use of a placebo arm. 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. Further, since all patients begin the placebo withdrawal period at the highest dose of study drug, a very effective or long-acting drug may still be effective even after the short 2–3 week withdrawal period and be interpreted as a negative study as the BP in the placebo group would not rise, such as was seen in the first pediatric ramipril study (R Portman, personal communication).

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 *(30)*. Figure 2 lists the various studies completed to date. The results of many, but not all, of the clinical trials of antihypertensive agents in children

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	No	Pending
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

Fig. 2. Clinical trials in pediatric hypertension. The list includes drug, trial design, sample size, dose response (yes/no), and label change (yes/no).

have resulted in publications in scientific journals *(31–43)*. 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 *(24)*. A recent review summarizes the advances in our knowledge about the use of antihypertensive agents in children and provides updated recommendations on the optimal use of antihypertensive agents in children and adolescents who require pharmacologic treatment *(30)*. Of note, however, most of these studies failed to show a dose response. As this pattern 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 *(44)*. Using meta-analytic techniques applied to the clinical trial data as submitted to the FDA, we determined that several factors are important which were predictive of trial success. These factors are discussed below.

Development and Use of a Liquid Formulation

Several of the trials of orally administered antihypertensive agents (particularly those used in the trials that failed to show a dose response) 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. An ideal oral drug for children should be effective, be well tolerated, have good stability, and have good palatability with acceptable taste, aftertaste, and smell. Modern medications are complex mixtures containing many other components besides the active ingredient. These are called "inert ingredients," or excipients and consist of bulk materials, flavorings, sweeteners, and coloring agents. These excipients increase the bulk, add desirable color, mask the unpleasant taste and smell, and facilitate a uniform mixture of the active ingredient in the final marketed preparation. Unlike the active ingredients, excipients are not well regulated in most countries. Although mostly well tolerated, some adverse events and idiosyncratic reactions are well known for a variety of excipients. These components play a critical role, especially in liquid and chewable preparations that are mostly consumed by infants and children *(45)*. Development of a liquid formulation is often challenging because bioavailability can be unreliable, and dissolving the agent in liquid can require high concentrations of alcohol. 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 which ultimately will affect drug compliance. Despite these issues, pediatric formulations should be requested in the Pediatric Drug Development Programs whenever possible. Development of these formulations is now more economically feasible because of benefits provided to companies for successfully completing trials requested by FDA as part of this program.

Primary Endpoint

Many successful trials used change in diastolic blood pressure (DBP) as the primary endpoint. Several unsuccessful studies (e.g., trials of amlodipine, irbesartan, and fosinopril) used change in sitting systolic blood pressure (SBP) as the primary outcome. We evaluated the reduction in SBP and DBP related to several agents and found that a reduction in DBP was more closely related to the dosage of agent administered. For example, in the enalapril trial where DBP elevation was the entry criteria, the dosage was more closely related to a reduction in DBP than SBP (coefficient 0.19 [P=0.001] versus coefficient 0.12 [P=0.08]).

We also observed a closer relationship between DBP reduction and dosage in the lisinopril trial (coefficient 0.12 [P=0.001] versus coefficient 0.08 [P=0.09]).

The reason for this closer relationship between DBP reduction and dosage may be related to the fact that there is less variability associated with measurement of DBP compared to SBP. DBP may have less physiological variability but also the change in DBP may be more difficult to detect by BP measurement. This reduction in variability may contribute to the success of DBP as the primary endpoint. Perhaps more likely is the fact that inclusion of DBP as a primary entry criteria tends to select children with secondary forms of hypertension. These patients are more likely to respond to drugs affecting the renin–angiotensin–aldosterone system, as seen with the lisinopril, enalapril, and losartan studies.

Systolic hypertension is however threefold more common in children and adolescents than diastolic hypertension, and the motivation to use SBP as the primary endpoint therefore likely derives from feasibility, a common problem in conducting pediatric drug trials. However, another important consideration is that SBP is a surrogate measurement that has been long accepted in adult patients because of its close relationship with hard endpoints of stroke, congestive heart failure, and myocardial infarction. These events are rare in children but the best BP correlate to any form of end-organ damage in children, i.e., left ventricular hypertrophy, is SBP. Thus, it seems that there would be definite benefit to the patient to test an antihypertensive medication for reduction in SBP. A primary study endpoint of mean arterial blood pressure that incorporates both SBP and DBP values might prove advantageous, and this possibility should be explored in future trials. Perhaps, even more beneficial would be the use of ambulatory BP monitoring in pediatric clinical trials for antihypertensive medications. One study has shown that the standard deviations of office casual blood pressure responses were up to 39% larger than those of ambulatory BP monitoring. Depending on the magnitude of the expected antihypertensive effect and trial design, the utilization of ABPM in antihypertensive drug efficacy studies may allow reduction of sample sizes by 57–75% *(46)*.

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 did not show a dose response, there was only a twofold difference between the high- 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, valsartan, and irbesartan trials, a similar pattern of lack of dose response was also seen with small dosing ranges at six-, eight-, and ninefold, 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. In some of these situations, there had been a conflict between FDA, investigators, and IRBs in this regard. The FDA has requested higher doses than approved in adults, leaving investigators and IRBs in a difficult situation of using a dose higher than its approval in adults. With the knowledge from these early trials, hopefully this issue will not arise in future trials.

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. These doses, however, were not included in the drug's label, making IRB approval of this high dose in a pediatric clinical trial problematic at the time.

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.

Another important aspect of early antihypertensive trials in children was that pharmacokinetic studies were often performed simultaneously with safety and efficacy trials and thus the information was not available for use in determining dosing. Under current pediatric drug development programs, these studies are performed before embarking on subsequent phase 3 trials in children.

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.

The fosinopril trial also failed to demonstrate a dose response, although it incorporated individual subject weight into the dosing. 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 milligram per kilogram basis was associated with blood pressure reduction.

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: lack of liquid formulation development, poor dose selection, and failure to fully incorporate weight and pediatric

pharmacology into trial design likely led to the difficulties observed in several antihypertensive pediatric exclusivity trials. The BP measurement to use as the primary endpoint of these trials remains controversial.

These data may be applicable to efforts to improve pediatric clinical trial design by government agencies, clinicians, and pharmaceutical sponsors in both North America and Europe. In the future, we recommend that pediatric antihypertensive trials do the following:

- 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,
- work with FDA/EU Paediatric Committee to design global pediatric trials by leveraging previous quantitative knowledge,
- routinely collect blood samples at informative time points to assess the pharmacokinetics in each subject to ascertain exposure–response analysis and perform these pharmacokinetic and pharmacodynamic trials before the initiation of safety and efficacy trials, and
- consider the use of ambulatory blood pressure monitoring to assess efficacy as part of the clinical trial design.

In addition, studies of the comparative effectiveness, long-term safety, and effects of antihypertensive agents on growth, maturation, and neurocognitive development are needed. Additional studies might also explore effects on vascular reactivity and the impact of pharmacologic treatment on long-term outcomes such as development of cardiovascular morbidity and mortality.

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Note: The letters 'f' and 't' following locators refer to figures and tables respectively.

From: *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*
Edited by: J. T. Flynn et al. DOI 10.1007/978-1-60327-824-9

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