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Pediatric Hypertension

Fourth Edition

Springer

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Editors

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Fourth Edition

With 94 Figures and 97 Tables

Springer

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Preface to the Fourth Edition

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

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

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

Seattle, WA, USA — Joseph T. Flynn
Boston, MA, USA — Julie R. Ingelfinger
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Preface to the Third Edition

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

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

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

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

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Preface to the Second Edition

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

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

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

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

Seattle, WA, USA — Joseph T. Flynn
Boston, MA, USA — Julie R. Ingelfinger
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Preface to the First Edition

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

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

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

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

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

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

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

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Part I

Regulation of Blood Pressure and Pathophysiologic Mechanisms of Hypertension

Neurohumoral and Autonomic Regulation of Blood Pressure

1

Jeffrey L. Segar

Abstract

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

Keywords

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

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Introduction

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

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

Overview of Autonomic Function

Vasoactive Sites in the Brain

Simplistically, arterial blood pressure is determined by total peripheral resistance, blood volume, and cardiac output. Peripheral resistance and cardiac output are governed by interacting neural, hormonal, and metabolic mechanisms signaling within the brain, end organs, and the vasculature. The central nervous system is particularly critical for cardiovascular homeostasis, as autonomic tone to the heart and vasculature is continuously modulated by afferent signals from the arterial baroreceptors and chemoreceptors acting upon cardiovascular centers within the brain. These centers, located between afferent and efferent pathways of the reflex arc, integrate a variety of visceral and behavioral inputs and in turn modulate a wide range of cardiovascular and metabolic responses (Spyer 1994). Studies using a number of investigational approaches identified that afferent fibers from baroreceptors and chemoreceptors, located within the carotid sinus, aortic arch, and carotid bodies, travel with the glossopharyngeal and vagal nerve and terminate within the medullary nucleus tractus solitarius (NTS) (Dampney et al. 2002). Second-order neurons originating from the NTS project to cardiac vagal motoneurons in the nucleus ambiguous and interneurons in the caudal ventrolateral medulla (VLM). Neurons that express a lot of gamma-aminobutyric acid (GABAergic neurons) from this area project to and inhibit sympathetic premotor neurons in the rostral ventrolateral medulla. Sympathetic neurons in the rostral VLM are tonically active, projecting to the intermediolateral cell column of the spinal cord and playing a critical role in maintaining sympathetic vasomotor tone.

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

Tonic Autonomic Activity

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

Though human data are lacking, animal studies suggest that the contribution of sympathetic drive to blood pressure changes during early development as well. The hypotensive response to ganglionic blockade may be used an as index of the neurally mediated contribution to blood pressure. Both alpha-adrenergic and ganglionic blockade, which inhibit end-organ responses to noradrenaline and sympathetic transmission at the ganglia, respectively, produce greater decreases in blood pressure in term fetal sheep than in preterm fetal sheep or newborn lambs, suggesting that fetal sympathetic tone is relatively high late in gestation (Tabsh et al. 1982; Vapaavouri et al. 1973). This hypotensive effect continues to decline with postnatal development (Vapaavouri et al. 1973). Sympathetic nerve efferents co-release norepinephrine and neuropeptide Y (NPY) from sympathetic varicosities, both of which exert potent pressor effects (Sanhueza et al. 2003). The peripheral vasoconstrictor effect resulting from sympathetic outflow is likely fine-tuned by opposing vasodilator influences, such as nitric oxide (NO). Whether sympathetic noradrenergic and peptidergic tone is more pronounced in late fetal life while nitric oxide dilation is enhanced postnatally is not known. In rats, the sympathetic nervous system appears much more immature at birth compared to sheep as ganglionic blockade in the first 24–36 h of life has no effect on resting blood pressure (Mills and Smith 1986). At an early age, ganglionic transmission appears to be the rate-limiting step in efferent sympathetic control, as the pressor response to tyramine, which stimulates norepinephrine release, is minimal. On the other hand, the vascular sensitivity to alpha-adrenoreceptor stimulation is enhanced immediately after birth, likely an adrenergic compensatory response.

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

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

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

Arterial Baroreflex

The arterial baroreflex plays a critical role in the short-term regulation of arterial pressure. Acute changes in vascular stretch related to alterations in blood pressure modify the discharge of afferent baroreceptor fibers located in the carotid sinus and aortic arch. Following central integration of these changes in afferent nerve traffic, efferent parasympathetic and sympathetic nerve activities are altered to influence heart rate and peripheral vascular resistance and buffer changes in arterial pressure (Abboud and Thames 1983; Persson et al. 1989). For example, a decrease in blood pressure results in a decrease in the baroreceptor firing rate, resulting in an increase in sympathetic vasomotor activity, and increase peripheral vascular resistance along with a decrease in cardiac vagal activity, resulting in increased cardiac output. Baroreflex control of heart rate is dominated by changes in cardiac vagal tone, although integrity of the reflex depends on both sympathetic and parasympathetic pathways (Yu and Lumbers 2000). Animal studies demonstrate that the arterial baroreflex is functional during fetal and early postnatal life (Booth et al. 2009; Brinkman et al. 1969; Itskovitz et al. 1983; Walker et al. 1978; Yardly et al. 1983). The observation that sinoaortic denervation produces marked fluctuations in fetal arterial pressure and heart rate further suggests the importance of the baroreflex to cardiovascular homeostasis in early development (Itskovitz et al. 1983; Yardly et al. 1983).

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

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

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

Developmental changes in baroreflex control of sympathetic outflow, primarily measured as renal sympathetic nerve activity (RSNA) responses to increases and decreases in blood pressure, have been examined. In chronically instrumented preterm fetal sheep (0.7 of gestation), baroreflex control RSNA was absent although pulse-synchronous bursts of RSNA were present (Booth et al. 2009). This same group demonstrated in slightly older sheep (123 days or 0.83 of gestation) that baroreflex-mediated inhibition but not excitation of RSNA was present (Booth et al. 2011b). This lack of sympathetic response to hypotension may have important implications in the ability of the fetus (or preterm infant) to adapt to low blood pressure. In studies of late-gestation fetal, newborn, and 4–6-week-old sheep, renal sympathoexcitation was present in response to hypotension, and in fact the sensitivity of the RSNA baroreflex function curve was greatest in the fetus and decreased during the postnatal period (Segar et al. 1992). Interestingly, studies in aging animals have shown that baroreflex control of heart rate and sympathetic nerve activity is impaired with senescence (Hajduczok et al. 1991b). Thus, the sensitivity of the baroreflex likely increases with early maturation, reaching a maximum sensitivity occurring during some developmental period, and then decreases with advancing age, an effect that may contribute to the development of hypertension.

Resetting of the Arterial Baroreflex

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

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

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

Cardiopulmonary Reflex

Cardiopulmonary receptors are sensory endings located in the four cardiac chambers, in the great veins, and in the lungs (Minisi and Thames 1991). In the adult, volume sensors mediating reflex changes in cardiovascular and renal function are believed to be primarily those residing in the atria (Goetz et al. 1991; Hainsworth 1991) and the ventricles (Minisi and Thames 1991), with the ventricular receptors being of utmost importance during decreases in cardiopulmonary pressures (Minisi and Thames 1991; Togashi et al. 1990; Victor et al. 1989). The majority of ventricular receptor vagal afferents are unmyelinated C fibers that can be activated by exposure to chemical irritants (chemosensitive) and changes in pressure or strength (mechanosensitive receptors) (Baker et al. 1979; Gupta and Thames 1983). These receptors have a low basal discharge rate which exerts a tonic inhibitory influence on sympathetic outflow and vascular resistance (Minisi and Thames 1991) and regulates plasma AVP concentration (Thames et al. 1980). Interruption of this basal activity results in increases in heart rate, blood pressure, and sympathetic nerve activity, whereas activation of cardiopulmonary receptors results in reflex bradycardia, vasodilation, and sympathoinhibition (Minisi and Thames 1991).

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

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

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

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

Peripheral Chemoreflex

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

Oxygen sensing in the carotid body is transduced by glomus cells, specialized sensory neurons that respond to hypoxia at higher PaO_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 (Carroll and Kim 2005). Recordings from carotid chemoreceptors in fetal sheep demonstrated responses to natural stimuli from ca. 90 days of gestation (Blanco et al. 1984, 1988b). Fetal carotid chemoreceptors were active and responsive to hypoxia, but only to changes in PaO_2 within the fetal range. Furthermore, the position of the response curve of the chemoreceptors to hypoxia was shifted to the left, and the sensitivity to an absolute change of arterial PO_2 was less compared to that of the adult.

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