Neurohumoral and Autonomic Regulation of Blood Pressure

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Abstract

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

Keywords

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

Contents

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

(Fletcher et al. 2006; Gardner et al. 2002; Hanson 1997; Herrera et al. 2012; Kane et al. 2012; Thakor and Giussani 2009a; Thakor et al. 2010). In fetal sheep, mild, acute acidemia (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 (Thakor and Giussani 2009a). To examine the effects of prevailing hypoxemia on responses to acute hypoxemia, Gardner et al. (2002) studied chronically instrumented fetal sheep grouped according to PaO_2. Functional chemoreflex analysis during early hypoxemia, performed by plotting the change in PaO_2 against the change in heart rate and femoral vascular resistance, demonstrated that the slopes of the cardiac and vasoconstrictor chemoreflex curves were enhanced in hypoxemic fetuses relative to control. Additional evidence suggests exposure to hypoxemia for a limited period of time (hours to days) has a sensitizing effect on the chemoreflex, whereas sustained hypoxemia (days to weeks) may have a desensitization effect (Hanson 1997). The mechanisms regulating this alteration in response are unclear. In the chick embryo, hypoxia increases sympathetic nerve fiber density and neuronal capacity for norepinephrine synthesis (Ruijtenbeek et al. 2000). Thus, augmented efferent pathways may contribute to the enhanced responses. On the other hand, recordings from carotid chemoreceptors in chronically hypoxic kittens demonstrate blunted responses to acute decreases in PaO_2 relative to control animals (Hanson et al. 1989). It is therefore possible that with prolonged hypoxia, blunting of the chemoreflex responses may be related to afferent mechanisms.

Although chemoreceptors are active and responsive in the fetus and newborn, studies in sheep and human infants suggest that chemoreceptor sensitivity and activity is reduced immediately after birth (Blanco et al. 1984; Hertzberg and Lagercrantz 1987). This decreased sensitivity persists for several days until the chemoreceptors adapt and reset their sensitivity from the low oxygen tension of the fetus to the higher levels seen postnatally (Hertzberg and Lagercrantz 1987; Kumar and Hanson 1989). The mechanisms involved with this resetting are not known, although the postnatal rise in PaO_2 appears crucial as raising fetal PaO_2 produces a rightward shift in the response curve of carotid baroreceptors to differing oxygen tension (Blanco et al. 1988b). Potential mechanisms within the glomus cell regulating developmental changes in O_2 transduction and chemoreceptor responses include, but are not limited to, anatomical maturation, developmental changes in oxygen-sensitive K^+ currents, adenosine responsiveness (Koos et al. 1995; Koos and Maeda 2001), dopamine and catecholamine turnover within the carotid body (Hertzberg et al. 1992), and differences in intracellular calcium mobilization during hypoxia (Carroll and Kim 2005; Sterni et al. 1995).

Sympathetic Activity at Birth

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

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

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

The change in environmental temperature at birth may play an important role in the sympathoexcitatory response at birth. Cooling of the near-term fetus both in utero and in exteriorized preparations results in an increase in heart rate, blood pressure, and norepinephrine concentrations, consistent with sympathoexcitation (Gunn et al. 1985; Van Bel et al. 1993). However, exteriorization of the near-term lamb fetus into a warm water bath does not produce the alterations in systemic hemodynamics or catecholamine values typically seen at birth (Van Bel et al. 1993). Fetal cooling, but not ventilation or umbilical cord occlusion, initiates nonshivering thermogenesis via neurally mediated sympathetic stimulation of brown adipose tissue (Gunn et al. 1991). In utero cooling of fetal lambs also produces an increase in RSNA of similar magnitude to that seen at delivery by cesarean section (Waldman et al. 1979), suggesting that cold stress plays a role in the activation of the sympathetic nervous system at birth. These changes occur before a decrease in core temperature and are reversible with rewarming, suggesting that sensory input from cutaneous cold-sensitive thermoreceptors rather than a response to a change in core temperature is mediating the response. The increases in heart rate, mean arterial blood pressure, and RSNA that normally occur at birth are absent in animals subjected to transection of the brain stem at the level of the rostral pons prior to delivery (Mazursky et al. 1996). These data suggest that supramedullary structures are involved in mediating the sympathoexcitation seen at birth. Additional studies, also in fetal sheep, demonstrate the paraventricular nucleus of the hypothalamus plays a vital role in regulating postnatal increases in sympathetic outflow and baroreflex function (Ellsbury et al. 2000). Given the known role of the hypothalamus in temperature and cardiovascular regulation, this structure is likely intimately involved in the regulation of circulatory and autonomic functions during the transition from fetal to newborn life (Gebber 1990).

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

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

Humoral Factors (See Also ▶ Chap. 2, "Vasoactive Factors and Blood Pressure in Children")

Renin-Angiotensin-Aldosterone System

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

The arterial baroreflex not only modulates heart rate and peripheral vascular tone, the reflex also regulates the release of vasoactive hormones, such as ANG II and AVP (Wood 1995). Changes in the levels of these circulating hormones, in turn, may influence neural regulation of cardiovascular function by acting at several sites along the baroreflex arc (Bishop and Haywood 1991). In the adult, peripheral ANG II facilitates activation of sympathetic ganglia and enhances the release and response of norepinephrine at the neuroeffector junction (Reid 1992). Within the central nervous system, ANG II stimulates sympathetic outflow and alters baroreceptor reflexes by acting on ANG II type 1 (AT_1) receptors located within the hypothalamus, medulla, and circumventricular organs (Bunnemann et al. 1993; Head and Mayorov 2001; Toney and Porter 1993). In the sheep fetus, the increase in arterial blood pressure produced by ANG II administration produces little or no cardiac slowing (Jones III et al. 1991; Robillard et al. 1982), although dose-dependent decreases in heart rate may occur (Ismay et al. 1979; Scroop et al. 1986). The bradycardic and sympathoinhibitory responses to a given increase in blood pressure are less for ANG II than for other vasoconstrictor agents (Segar et al. 1994b).

Endogenous brain ANG II appears to contribute little to basal arterial pressure in fetal sheep though appears active postnatally. Lateral ventricle administration of an AT_1 receptor antagonist has no effect in the fetus but lowers blood pressure and resets the baroreflex toward lower pressure in newborn and 8-week-old sheep at doses that have no effect when given systemically (Segar et al. 1997). However, lateral ventricle injection of ANG II increases blood pressure in the fetus, an effect blocked by AT_1 receptor antagonists (Shi et al. 2005; Xu et al. 2003, 2004). Increased blood pressure via activation of angiotensin receptors was associated with elevated c-fos expression (a marker of neuronal activation) in numerous cardiovascular areas known to be AT_1 receptor abundant (Shi et al. 2005; Xu et al. 2003, 2004). An endogenous local RAAS in the brain, including ACE, also appears to be functional in the fetus, as intracerebroventricular injection of ANG I increases blood pressure and c-fos expression in the supraoptic nucleus and paraventricular nucleus (Shi et al. 2010).

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

(Segar et al. 1994a). Two- to fourfold higher levels of ANG II in the newborn than in fetal or adult sheep may help explain these observations (Robillard et al. 1982). Similarly, in the newborn lamb, angiotensin-converting enzyme inhibition or AT_1 receptor blockade decreases RSNA and heart rate and resets the baroreflex toward lower pressure (Segar et al. 1994b, 1997). Resetting of the reflex is independent of changes in prevailing blood pressure.

Arginine Vasopressin

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

In several adult species, AVP modulates parasympathetic and sympathetic tone and baroreflex function (Berecek and Swords 1990; Bishop and Haywood 1991; Luk et al. 1993; Nuyt et al. 1996). Administration of AVP evokes a greater sympathoinhibition and bradycardia than other vasoconstrictors for a comparable increase in blood pressure, this effect being attributed to AVP enhancing the gain of the reflex and resetting it to a lower pressure (Bishop and Haywood 1991; Luk et al. 1993). However, in fetal and newborn sheep, sequential increases in plasma AVP do not alter heart rate or RSNA baroreflex responses to acute changes in blood pressure (Nuyt et al. 1996).

Endogenous AVP has little effect on baroreflex function early during development. Peripheral administration of a V_1 receptor antagonist has no measurable effects on resting hemodynamics in fetal sheep or on basal arterial blood pressure (Ervin et al. 1992), heart rate, RSNA, or baroreflex response in newborn lambs (Nuyt et al. 1996). This lack of baroreflex modulation by AVP may facilitate the pressor response to AVP in fetuses and newborns during stressful situations such as hypoxia and hemorrhage, which may be particularly important for maintaining arterial pressures during these states early in development.

The role of central AVP in maintaining hemodynamic homeostasis in the developing animal has not been extensively studied. Under basal conditions, fetal AVP levels are tenfold higher in the cerebrospinal fluid than in plasma, suggesting AVP contributes to central regulation of autonomic function (Stark et al. 1985). Intracerebroventricular infusion of AVP produces significant decreases in mean arterial blood pressure and heart rate in newborn lambs although no reflex changes in RSNA are seen (Segar et al. 1995). The changes in blood pressure and heart rate are completely inhibited by administration of an AVP receptor type 1 (V_1) antagonist, demonstrating that central cardiovascular effects of AVP are mediated by V_1 receptors, as has been reported in mature animals (Unger et al. 1987).

Glucocorticoids

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

pressure (Tangalakis et al. 1992; Unno et al. 1999). Antenatal exposure to exogenous glucocorticoids increases fetal and postnatal arterial blood pressure by enhancing peripheral vascular resistance and cardiac output without altering heart rate (Derks et al. 1997; Padbury et al. 1995; Stein et al. 1993). The use and effectiveness of hydrocortisone for hypotension in preterm and term neonates is well described (Ng et al. 2006; Seri et al. 2001). However, the mechanisms accounting for the increase in blood pressure and vascular resistance are not clear. In the adult, administration of hydrocortisone or dexamethasone suppresses resting and stimulated muscle sympathetic nerve activity, suggesting little role for augmented sympathetic tone (Dodt et al. 2000; Macefield et al. 1998). In contrast, glucocorticoids enhance pressor responsiveness and vascular reactivity to norepinephrine and angiotensin II (Grünfeld and Eloy 1987; Grünfeld 1990), in part by increasing α1-adrenergic and AT_1 receptor levels and potentiating angiotensin II and vasopressin-induced inositol triphosphate production (Provencher et al. 1995; Sato et al. 1992). Glucocorticoids also reduce the activity of depressor systems, including vasodilator prostaglandins and nitric oxide, and have been shown to decrease serum $NO2^{-}/NO3^{-}$, endothelial nitric oxide synthase mRNA stability, and protein levels (Wallerath et al. 1999).

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

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

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

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

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

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

Nitric Oxide

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

Reactive Oxygen Species

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

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

Autonomic Function During Human Development

In human neonates and children, autonomic function has most simplistically been studied by examining changes in heart rate, various indices of heart rate variability, and blood pressure in response to postural changes which unload (head-up position) or load (head-down position) arterial baroreceptors. Some investigators have been unable to demonstrate a consistent response of heart rate during the neonatal period to tilting and concluded that the heart rate component of the baroreflex is poorly developed early in life, while others have demonstrated in healthy preterm and term infants that unloading arterial baroreceptor by head-up tilting produces a significant heart rate response (Picton-Warlow and Mayer 1970; Thoresen et al. 1991; Waldman et al. 1979). Using venous occlusion plethysmography, Waldman et al. (1979) found in healthy preterm and term infants that 45° head-up tilting produced no significant tachycardia, although a mean 25% decrease in limb blood flow was observed, suggesting increased peripheral vascular resistance. In contrast, Meyers et al. found that 1–2-day-old healthy, term newborns display changes in heart rate with head-up and head-down tilt similar to those observed in the adult (Myers et al. 2006). Interestingly, at 2–4 months of age, the increase in heart rate to unloading of baroreceptors (head-up tilt) is lost (Fifer et al. 1999; Myers et al. 2006). The change in heart rate parasympathetic cardiac response to standing increased in children 6–19 years of age (Yamanaka and Honma 2006; Zhao et al. 2015).

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

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

More recently, the use of noninvasive blood pressure techniques, primarily plethysmography, has further advanced our understanding of autonomic functional changes with maturation. Using this technique to examine sequences of spontaneous changes in blood pressure and heart rate in infants 24-week gestational age to term, Gournay et al. reported baroreflex sensitivity increased with gestational age and in premature infants <32-week gestation with postnatal age (Gournay et al. 2002). In contrast, Witcombe et al. found that preterm infants, but not term infants, when first studied at 2–4-week corrected age, had no maturational increase in spontaneous baroreflex sensitivity over the next 6 months of life (Witcombe et al. 2012). Differential rates of maturation in preterm and term infants of parasympathetic contributions to heart rate, which falls in the first month of life, followed by progressive increases between 1- and 6-month postnatal age, may contribute to these findings. In term infants studied over the first 6 months of life, Yiallourou et al. found that spontaneous baroreflex sensitivity was decreased in prone compared to supine infants at 2–3 and 5–6 months of age, parasympathetic control of heart rate strengthened with postnatal age while sympathetic vascular modulation decreased (Yiallourou et al. 2011, 2012). Preterm infants showed similar maturational changes in parasympathetic and sympathetic modulation of end-organ responses, though even when corrected for postmenstrual age, preterm infants displayed reduced parasympathetic and sympathetic modulation of heart rate and blood pressure, respectively (Yiallourou et al. 2013).

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

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

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

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

Conclusion

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

Cross-References

► Vasoactive Factors and Blood Pressure in Children

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