Hypertension is often viewed solely as a disease of the adult. However, early indicators of hypertension are frequently observed in young children and neonates. Having an adequate appreciation of the normal range of infant blood pressure is critical for the appropriate management of the conditions associated with elevated or abnormally low blood pressure. In healthy neonates, systolic blood pressure increases rapidly during the first 6 weeks of life with the most rapid rise observed during the first 5 days. A similar pattern is observed for diastolic pressures. The observed increases in blood pressure are positively correlated with birth weight and both gestational and postnatal age. The incidence of hypertension in the neonate has been reported to range from 0.2% to 2.6% and is frequently an indicator of other renal or cardiovascular abnormalities. Systemic hypotension is reported in 24% to 45% of very low birth weight infants and is frequently caused by hypovolemia. The regulation of blood pressure is complex and the mechanisms involved remain to be fully elucidated. The results of several investigations into the molecular mechanism(s) of hypertension are considered.

The Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure defines normal blood pressure in individuals 18 years and older as a systolic blood pressure (BP) <120 mm Hg and a diastolic BP <80 mm Hg. Systolic BP from 120 to 139 mm Hg or diastolic BP from 80 to 99 mm Hg is prehypertension, systolic BP from 140 to 159 mm Hg, or diastolic BP from 100 to 109 mm Hg is Stage I hypertension, while systolic BP >160 mm Hg or diastolic BP >110 mm Hg is Stage 2 hypertension. In infants and children less than 18 years of age, normal BP is defined as systolic and diastolic BP greater than the 10th percentile and less than the 90th percentile adjusted for age, height, and sex. High-normal BP is defined as average systolic or diastolic BP greater than or equal to the 90th percentile but less than the 95th percentile. Hypertension is defined as average systolic or diastolic BP greater than or equal to the 95th percentile adjusted for age, height, and sex measured on at least 3 separate occasions.

Because of concerns regarding mercury toxicity, nonmercurial automated sphygmomanometers have gained popularity. The recommended method to measure blood pressure is via a sphygmomanometer, placed at the heart level, after 3 to 5 minutes of rest in the seated position. With the cuff of appropriate size placed around the right arm, one listens to the Korotkoff sounds with a stethoscope on the brachial artery at the cubital fossa of the right arm. The systolic blood pressure is the appearance of the first Korotkoff sound while the 5th Korotkoff sound (disappearance of Korotkoff sounds) is the diastolic blood pressure. The averages of at least 2 readings are taken as the blood pressure levels.

Although the reliability of automated devices is not clear, especially in children, BP has been measured indirectly using oscillometric manometers. In the newborn, a cuff width-to-arm circumference ratio between 0.45 and 0.55 has been shown to increase the accuracy of indirect blood pressure measurements (compared with direct pressure measurements) with mean blood pressures between 25 to 50 mm Hg. However, in critically ill low-birth weight infants, oscillometric blood pressures may not be reliable and therefore, direct blood pressure measurement is recommended. In the setting of the intensive care nursery, blood pressure is recorded directly via the umbilical or peripheral
Regulation of Blood Pressure

Blood pressure is generally expressed as the product of cardiac output and peripheral resistance. However, the relationship between pressure and flow in blood vessels is not linear and the control mechanisms for pressure regulation involve more than simply a direct change in either cardiac output or peripheral resistance. Blood flow through a vessel is determined by 2 primary factors: the amount of pressure forcing the blood through the vessel, and the resistance to flow. The resistance to flow in a blood vessel is best described as impedance because this takes into account inertial properties and viscosity of blood elastic properties of blood vessels, and the variable geometries of blood vessels during phasic flow. One of the most important factors influencing the flow through the arteries is the vessel diameter, because the conductance is proportional to the fourth power of the diameter. Therefore, flow is influenced more by changes in vascular resistance than by pressure changes.

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

The low systolic blood pressure at birth, due to low cardiac output and peripheral resistance, increases rapidly in the first 6 weeks of life (especially in the first 5 days), remains at a constant level until age 6 years, and increases gradually until age 18 years. The pattern is similar for diastolic blood pressure except that there is a slight decrease in diastolic blood pressure in the first 6 months of life (relative to the blood pressure in the first week of life). The transient decrease in diastolic blood pressure in the first 6 months of life is associated with a low intestinal vascular resistance, mediated by nitric oxide. The increase in blood pressure with age in preterm infants occurs as a function of postconceptional age. After 70 years of age, systolic BP continues to increase but diastolic BP may decrease.

The increase in blood pressure with age is caused by a rise in both cardiac output and total peripheral resistance. The age-related changes in vascular resistance are selective since in the perinatal period there is a rapid fall in resistance in the lungs, small intestines, brain, and the kidney. Moreover, the increase in regional blood flow with age cannot be accounted for by an increase in blood pressure. Indeed, in the immediate perinatal period, the increases in regional blood flow with postnatal age is independent of blood pressure. In the newborn, cardiac output is increased mainly by accelerating heart rate. The high heart rate may be due to differential sympathetic and parasympathetic effects, hypersensitivity of the cardiac receptors, and peripheral vasodilatation. The low precapillary resistance and low venous capacitance are conducive to high systemic blood flow per unit body weight, and provide increased tissue perfusion for growth.

Blood Pressure in Healthy Full-term Infants

Having an adequate appreciation of the normal range of infant BP is crucial for the appropriate management of conditions associated with elevated or low BP. Numerous studies have been conducted in an attempt to determine the range of BPs and rate of change in term and pre-term infants. Although there are few studies documenting the changes in BP with postconceptional age in the first few hours and days of life, blood pressure is positively correlated with birth weight and both gestational and postnatal age with a marked increase in the first 5 days of postnatal life. A nomogram for BP as a function
of gestational age and birth weight in the first 3 days of life has been constructed. The fact that BP is about 6 to 10 mm Hg higher in awake than in sleeping babies is not factored in this nomogram. These data mirror those of an earlier study in which the BP of infants was monitored during the first 96 hours after birth, (see Table 1). BP at three years of age correlated with length rather than weight. Indeed, the nomograms of BP have height as an important variable. In adults, systolic BP is higher in the lower than in the upper extremities. However, in healthy newborns, calf BP has been reported to be 1 to 3 mm Hg lower than arm blood pressures. Calf BPs begin to exceed arm blood pressures by 6 months of age.

**Systemic Hypertension**

The definition of hypertension (>95th percentile) in infants and children, patterned from adults with essential hypertension, has been criticized for lack of biological significance. In the first week of life, the 95th percentile level of systolic blood pressure is 95 to 96 mm Hg and 104-113 mm Hg from 2 to 6 weeks of age. The incidence of hypertension in the newborn period has been reported to vary from 0.2% to 2.6%. Hypertension in the newborn is often an indicator of other renal (thrombosis/infarction, parenchymal disease, obstructive uropathy) or cardiovascular-related problems (patent ductus arteriosus, coarctation of the aorta). Older literature suggests that the risk of developing hypertension is increased by umbilical artery catheterization and subsequent renal embolism. Thrombosis has been found in 81% percent of infants with indwelling umbilical artery catheters. A high incidence of hypertension is also found in infants with bronchopulmonary dysplasia (43%). Rarer causes may be secondary to neonatal pharmacotherapy (eg, steroids) and maternal drug use (eg, cocaine). Many hypertensive infants subsequently become normotensive by 1 year of age and most babies no longer need antihypertensive therapy by 2 years of age. However, there are also reports of significant morbidity and mortality related to hypertension. The drugs to use in the neonatal period have not been standardized and many have not been officially approved for use in this age group. It has been suggested that in the absence of symptoms and/or organ involvement, blood pressure less than 99th percentile should not be treated with drugs.

**Treatment.** There are no drugs approved for the treatment of neonatal hypertension. However, there are some prospective reports on the use of several antihypertensive agents. For example, nicardipine, given as an intravenous infusion (0.5 μg/kg/min) decreased blood pressure by about 20%. There are case reports of the use of angiotensin converting enzyme inhibitors in the treatment of hypertension in the newborn. Enalaprilat can be given intravenously at a dose of 15 μg/kg/min over a 5- to 10-minute period and can be repeated every 8 to 24 hours. Oral enalapril and captopril (0.01 mg/kg as a starting dose) have also been used. Some drugs

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**Table 1. Mean Blood Pressures (MBP) and 10th Percentiles by Birth Weight and Postnatal Age**

<table>
<thead>
<tr>
<th>Birth Weight (grams)</th>
<th>3</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72</th>
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<td>36/24</td>
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<td>38/26</td>
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<tr>
<td>600</td>
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<tr>
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<tr>
<td>800</td>
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<tr>
<td>900</td>
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<td>39/27</td>
<td>40/29</td>
<td>42/30</td>
<td>43/31</td>
<td>45/33</td>
<td>46/34</td>
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</tr>
<tr>
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<td>39/27</td>
<td>40/28</td>
<td>41/29</td>
<td>42/31</td>
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<tr>
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<td>46/35</td>
<td>48/36</td>
<td>49/47</td>
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</table>

NOTE. The first set of numbers is the MBP at the given weight and postnatal age and the second figure is the tenth percentile. Reprinted with permission.
used to treat hypertensive emergencies in older children and adults that should probably be avoided include diazoxide, nifedipine, and sodium nitroprusside. The duration and magnitude of action of diazoxide and nifedipine may be unpredictable; thiocyanate levels in the newborn may be unreliable as an indicator of nitroprusside toxicity.\textsuperscript{14} β-adrenergic blockers may need to be avoided because many newborns with hypertension have chronic lung disease.

Systemic Hypotension

Systemic hypotension has been reported to be present in 24\% to 45\% of very low birth weight infants.\textsuperscript{15} In the treatment of neonatal hypotension, blood pressure is the primary endpoint. However, intact organ blood flow autoregulation is best thought to define the physiologic range of blood pressure.\textsuperscript{16} The effects of ductal and atrial shunts on left and right ventricular output, respectively, have marked influences on systemic flow. Because flow to the upper body, including the brain, is not affected by ductal and atrial shunts in the premature babies in the perinatal period, superior vena cava flow (SVC) has been claimed to be a better end point than blood pressure in the management of hypotensive preterm infants. Indeed, SVC flow correlated well with middle cerebral artery flow and peri/intraventricular hemorrhage.\textsuperscript{17,18} SVC is measured by color Doppler sonography and the lower limits of normal has been defined as 30, 34, 42, and 46 mL/kg/min respectively at 5, 12, 24, and 48 hours of age.

Systemic hypotension in preterm infants is caused predominantly by absolute hypovolemia, as well as abnormal regulation of peripheral vascular resistance (eg, septic shock), and myocardial dysfunction, alone or in combination. Even in the absence of definitive evidence of hypovolemia, the initial treatment of hypotension usually includes fluid administration (normal saline given at 10-20 mL/kg over 15-30 minutes). If blood pressure or SVC flow is not normalized, pressor agents are added to the treatment. The agent of choice to increase cardiac output, blood pressure, or systemic blood flow in the preterm neonate is not yet settled.\textsuperscript{16-18} By using SVC flow as the primary end point, dobutamine was deemed more beneficial than dopamine in increasing systemic blood flow.\textsuperscript{19} However, death rates and peri/intraventricular hemorrhage were not different between the 2 treatment groups.

Inotropes and Receptors

Dobutamine. (+)-dobutamine is a β\textsubscript{1}-adrenergic agonist and α\textsubscript{1}-adrenergic antagonist, while (-)-dobutamine is α\textsubscript{1}-adrenergic agonist and 10× less potent than (+)-dobutamine as a β\textsubscript{1}-adrenergic receptor agonist. Clinically used dobutamine has both enantiomers. Thus, depending upon which receptor is stimulated, cardiac output may increase but blood pressure may decrease. The β\textsubscript{2}-adrenergic agonist properties of dobutamine,\textsuperscript{20} by dilating systemic arteries may contribute to the decrease in blood pressure.

α\textsubscript{1}-Adrenergic receptors. Mammals express 3 α\textsubscript{1}-adrenergic receptors: α\textsubscript{1A} (designated as α\textsubscript{1C} when it was originally cloned), α\textsubscript{1B}, and α\textsubscript{1D}. α\textsubscript{1A} and α\textsubscript{1D} but not α\textsubscript{1B} adrenergic receptors have been shown to regulate adult blood pressure.\textsuperscript{21-24} Vascular beds may have receptor subtype specificity. The α\textsubscript{1A} receptor subtype may govern the contraction of renal and caudal arteries, whereas α\textsubscript{1D} adrenergic receptors may regulate the contraction of the aorta, femoral, iliac, and superior mesenteric arteries. Hypertrophy in neonatal cardiac myocytes is mediated primarily by α\textsubscript{1A} and α\textsubscript{1B} adrenergic receptors. Aortic hypertrophy, on the other hand, is primarily due to the actions of the α\textsubscript{1D} adrenergic receptors.

α\textsubscript{2}-Adrenergic receptors. Mammals express three α\textsubscript{2}-adrenergic receptors: α\textsubscript{2A}/D, α\textsubscript{2B}, and α\textsubscript{2C}.\textsuperscript{21} The α\textsubscript{2A} adrenergic receptors mediate the majority of the classical effects of α\textsubscript{2} adrenergic stimulation (auto receptor function and decrease in blood pressure). The α\textsubscript{2B} adrenergic receptors, in contrast, are predominantly found outside of the central nervous system at extrajunctional or postsynaptic sites, produce vascular constriction and thus counteract the hypotensive effects of α\textsubscript{2A} adrenergic receptor stimulation. The α\textsubscript{2C} adrenergic receptors do not have cardiovascular effects but may play a role in mediating the hypothermic response.

β-Adrenergic receptors.\textsuperscript{21,25-27} The disruption of either the β\textsubscript{1} or the β\textsubscript{2}-adrenergic receptor, both, or even the β\textsubscript{1}, β\textsubscript{2}, and β\textsubscript{3}-adrenergic receptors, does not affect heart rate or resting blood pres-
pressure in mice. Mice that lack the β1-adrenergic receptor are unresponsive to cardiac β-adrenergic receptor stimulation, suggesting that neither β2- nor β3-adrenergic receptors play a role in the inotropic or chronotropic responses in the mouse. The hypotensive response to isoprotrenol, however, is impaired in both β1 and β2-adrenergic null mice. The β3-adrenergic receptors do not have major effects on the cardiovascular system. An allelic variant of α2C (Δ322-325) with β1 adrenergic receptor (Arg389) may increase the risk of heart failure in blacks, but the role these variants may play in the newborn is not known.

**Dopamine.** Presynaptic/junctional and postsynaptic/dopamine receptors are found in many organs and vascular beds. Dopamine receptors have also been described in the heart but their function is at present unknown. Dopamine also modulates fluid and sodium intake, via its actions in the kidney and gastrointestinal tract, and by the regulation of cardiovascular centers that control the functions of the heart, arteries, and veins. Abnormalities in dopamine production and receptor function accompany a high percentage of human essential hypertension and several forms of rodent genetic hypertension. Allelic variants of genes that encode the regulators of the dopamine receptors, alone or in combination with genetic variants that encode regulatory proteins of the renin angiotensin system, are associated with human essential hypertension.

**Dopamine receptors.** The circulating levels of dopamine are in the picomolar range and are far too low to stimulate its own or other receptors. Dopamine stimulates its own receptors at nanomolar concentrations. At low micromolar concentrations, dopamine also stimulates β-adrenergic receptors, but at 4 to 16 times the concentration of dobutamine. At low to high micromolar concentrations, dopamine may also occupy α-adrenergic and serotonin receptors. Variants of dopamine receptors can affect their function. There are two classes of dopamine receptors; the D1-like receptors which are the D1 and D5 receptors (also known as DA1 and DA5, respectively, in rodents) and the D2-like receptors—the D2, D3, and D4. The D1-like receptors are vasodilatory while the D2-like receptors are mediators of vasodilation or vasoconstriction depending upon the starting vascular resistance. When vascular resistance is high, the D2-like receptors act as vasodilators by the inhibition of norepinephrine release. However, when vascular resistance is low, D2-like receptors mediate vasoconstriction probably via the D3 receptor.

**G protein-coupled receptor kinases.** Variations in the expression or function of G protein-coupled receptor kinases (GRK) have been found to affect the function of the β-adrenergic and dopamine receptors. The effect of these variations on responses in the newborn is unknown. Increased activity of GRK2 in blood vessels and in the heart decreases the function of G protein-coupled receptors, including β1- and β2-adrenergic receptors. We have reported that variants of GRK4 are responsible for the decreased responsiveness of the D1 dopamine receptor in the kidney in essential hypertension. Because GRK4 is not expressed in vascular smooth muscle cells GRK4 gene variants may not be responsible for any decreased effects of D1 receptors in the newborn. However, GRK4 is expressed in the heart (unpublished data). As noted, individuals that are homozygous for α2C Δ322-325-adrenergic receptor may be at increased risk of developing heart failure. Although the α2C Δ322-325-adrenergic receptor has decreased function, the disruption of the α2C-adrenergic receptor in mice does not lead to any cardiovascular phenotype. It is possible that increased activity of GRK2, GRK4, and GRK5 in the heart which is developmentally-related or acquired may be responsible for decreased effects of inotropic agents in the newborn.

**Cardiac output, blood pressure, and vascular sensitivity and reactivity to catecholamines with age.** As stated, the increase in blood pressure with age is due to a rise in both cardiac output and total peripheral resistance. Age-related changes in vascular resistance are selective since in the perinatal period there is a rapid fall in resistance in the lungs, small intestines, brain, and the kidneys while resistance increases in the femoral vessels. The increase in femoral resistance with age is probably related to both an increase in vascular reactivity to vasoconstrictors and developmental alterations in vascular smooth muscles.

**α-adrenergic receptors.** The positive inotropic effect of α-adrenergic receptor stimulation is less in the newborn (rabbits and rats) than in the adult. In contrast, the positive chronotropic effect of α-adrenergic receptor stimulation in
the newborn is greater in neonatal puppies than adult dogs. The neonatal renal and cerebral circulations are also more sensitive to α-adrenergic stimulation in dogs, pigs, guinea pigs, and baboons. The increased α-adrenergic receptor effects are correlated with increased α-adrenergic receptor density and post receptor events that may be vessel specific. It is possible that the changes in α-adrenergic receptor responsiveness with maturation are mediated by the differential maturation of α-adrenergic receptor subtypes, signal transduction, or effector proteins. However, except in the rat, the molecular biological class of these receptors during development has not been studied.

β-adrenergic receptors. In the heart, responses to β-adrenergic stimulation increase with age. However, in many species the myocardial β-adrenergic response is associated with a decrease in β-adrenergic density. The decline in cardiac β-adrenergic receptor density with age is accompanied by an increase in maximum adenylyl cyclase response to β-adrenergic stimulation. However, the neonatal heart is resistant to β-adrenergic receptor desensitization compared to the adult that is not caused by decreased function of GRK2; agonist treatment actually produces sensitization. This would suggest, the decreased β-adrenergic effect in the neonates is not due to increased activity of GRK2.

During the newborn period, in several vascular beds, β2-adrenergic vasodilatory effects are enhanced. Many preterm neonates (humans and baboons) may fail to complete the complex adrenal adaptive response that occurs at birth and develop adrenal insufficiency. Hydrocortisone has been shown to increase arterial pressure in hypotensive preterm neonates resistant volume expansion and vasopressor therapy. This pressor-resistant hypotension could be caused by down-regulation of adrenergic receptor abundance or function and a relative or absolute adrenal insufficiency. Therefore, measurement of cortisol levels in volume-and pressor-resistant infants may identify those with cortisol deficiency as a contributing factor to their hypotension.

Dopamine receptors. Dopamine increases renal blood flow without affecting cerebral hemodynamics in preterm infants. The effect of dopamine on intestinal blood flow in this age group is not consistent. In contrast to the apparent ability of dopamine to increase renal blood flow in the preterm human, in other mammals (dog, pig, and rabbit), the renal vasodilatory effect of dopamine and the coupling of D1-like receptors to their effector proteins is less in the young compared to the adult. We would like to suggest that the increase in renal blood flow with dopamine in the newborn humans may arise, in part, by occupation of renal β-adrenergic receptors. Serotonin also variably affects renal blood flow, depending upon the receptor subtype involved and species. Because serotonin-2 receptors induce renal vasodilation, via nitric oxide, and the nitric oxide effect is increased in the newborn kidney, a dopaminergic action on serotonin receptors may also explain the ability of dopamine to increase renal blood flow in the newborn. These effects and the increase in cardiac output and systemic pressure with dopamine may explain the ability of dopamine to increase renal blood flow in the newborn, in spite of the “immaturity” of dopamine receptor function. In endotoxin shock in piglets, dopamine caused a greater deterioration in renal function than volume replacement alone.

Corticosteroids. Many preterm neonates (humans and baboons) fail to complete the complex adrenal adaptive response that occurs at birth and develop adrenal insufficiency. Hydrocortisone has been shown to increase arterial pressure in hypotensive preterm neonates resistant volume expansion and vasopressor therapy. This pressor-resistant hypotension could be caused by down-regulation of adrenergic receptor abundance or function and a relative or absolute adrenal insufficiency. Therefore, measurement of cortisol levels in volume-and pressor-resistant infants may identify those with cortisol deficiency as a contributing factor to their hypotension.

Summary

Great caution should be exercised when comparing the BP measurements obtained in different studies. Measurement of blood pressures in neonates, especially the low birth weight and pre-term neonates, is extremely difficult. The maturation of receptors (adrenergic, dopaminergic, and serotonergic receptors) that regulate cardiac and vascular function affects the response of the newborn to inotropes and vasoactive agents acting on these receptor subtypes. It is also possible that nonresponsiveness to these drugs may not only be related to “immaturity” but also because of the presence of gene variants that produce receptors with decreased function and may cause an increase or a decrease in blood pressure. Additionally, func-
tional immaturity of the adrenal glands may cause refractory hypotension, which is independent of dopamine and adrenergic receptor function.

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