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Cardiovascular and Autonomic Influences on Blood Pressure

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INTRODUCTION

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

CONTROL OF BLOOD PRESSURE

Although the relationship between pressure and flow through the vascular tree is not linear, BP can be expressed as the product of cardiac output (CO) and peripheral resistance (1) (Table 1). These variables are closely intertwined, and the control mechanisms for pressure regulation involve more than simply a direct change in either CO or peripheral resistance (2). The major determinant of BP at rest is arteriolar resistance; during exercise, CO assumes a more important role.

Cardiac Output

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

Table 1
Factors Influencing Arterial Pressure as the Product of Cardiac Output and Peripheral Resistance

<i>Cardiac output</i>
Heart rate
Stroke volume
Venous return
Myocardial contractility
Blood volume
<i>Peripheral resistance</i>
Adrenergic nerves
Circulating catecholamines
Other vasoactive substances
Acetylcholine
Angiotensin II
Endothelium-derived contracting factor
Kinins
Neuropeptides (neurotensin, NPY, substance P)
Nitric oxide
Oxytocin
Prostanoids (prostaglandins, HETEs, leukotrienes, thromboxanes)
Serotonin
Vasopressin (antidiuretic hormone)
Ions and cellular regulators (e.g., calcium, sodium, chloride, potassium, magnesium, manganese, and trace metals, pH, etc.)
Hematocrit (viscosity)
Reactive oxygen species

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CO varies widely depending on metabolic and physical activity, age, and size of the body. For healthy young males, resting CO is 5.6 L/min. The value is 20% less in females. As this value varies consistently with the surface area of the body, it is also expressed as cardiac index, which is the CO per square meter of body surface area. This value is about 3 L/min/m². Babies have a higher cardiac index at 5.5 L/min/m², and this value is even higher in preterm babies.

Control of CO is governed by two kinds of mechanisms: primary mechanisms, which operate quickly for acute regulation, and secondary mechanisms, which have a slower onset and regulate long-term aspects of cardiac function. CO is derived from the product of stroke volume (volume represented by the volume of blood pumped by the heart in one beat) and the heart rate (HR) per minute. In infancy and early childhood, CO is increased mainly by an increase in HR because the capacity of the cardiac muscle to increase stroke volume during this period is limited.

Stroke Volume

Stroke volume depends on three primary factors, all of which are interrelated and not mutually exclusive. These factors are preload, afterload, and myocardial contractility. Preload is determined by venous filling of the right ventricle and, subsequently, the left ventricle, determining the volume of blood available to be pumped. Preload is classically compromised in dehydration and hemorrhage. Afterload is determined by peripheral arterial resistance and intrinsic ventricular wall stress. Afterload determines diastolic pressure and, by extension,

mean arterial pressure and tissue perfusion. Afterload is reduced in septic shock with profound vasodilatation, and it is increased in hypothermia. Myocardial contractility is defined as the inherent ability of cardiac muscle to pump blood. This function is compromised in myocarditis and some forms of cardiomyopathy. These primary factors could be altered by secondary factors in response to the physiological state of the individual.

Preload

CO is determined primarily by preload, that volume of venous blood that fills the ventricle during diastole. This is also called venous return or end diastolic volume. The adult heart is capable of pumping up to 15 L/min, but the usual resting CO is only 5.6 L/min. The Frank-Starling law describes the inherent ability of the heart to regulate its output despite a rapidly varying venous return. Increasing venous return increases end-diastolic volume resulting in the stretch of the muscle fibers. Consequently, increased volume at the end of diastole leads to immediate, increased, and effective ejection during systole, which is defined as increased stroke volume. This ensures that even when end-diastolic volume or filling is increased, the end-systolic volume, or the volume of blood left in the ventricle does not increase, as all the extra volume is pumped out. The energy output of a heart muscle fiber increases with increasing fiber length up to a point, beyond which further extension of the fiber results in a decrease in its contractile force, which then causes a reduction in stroke volume. An important aspect of the Frank-Starling law is that a change in the afterload (or outflow resistance) has almost no influence on cardiac output. Preload-dependent regulation of stroke volume is also called *heterometric regulation*. Stretching of the ventricle stretches the sinus node in the wall of the right atrium, which increases its rate of firing, and increases the HR by 10–15%. The stretched right atrium also initiates a reflex called the Bainbridge reflex, which increases HR. In summary, increasing preload increases stroke volume and HR. Therefore, preload is a major factor in the enhancing of CO.

Afterload

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

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

$$EF = SV/LVEDV$$

This can be quantified with echocardiography by measuring the shortening fraction of the muscle fiber, which correlates directly with contractility. Typically, the EF for a normal adult

is 0.50–0.75. This fraction does not change with gestational or postnatal age. Left and right ventricular diastolic volumes, however, increase with gestational and postnatal age (3).

Myocardial Contractility

Myocardial contractility accounts for the increases in contractile force of a muscle fiber, with no accompanying change in fiber length. This capacity of cardiac muscle is called *homeotropic regulation*. The heart is richly supplied with both sympathetic and parasympathetic nerves that have profound effects on heart rate and contractility. The resting normal sympathetic tone maintains cardiac contractility at 20% greater than in the denervated heart. Increased sympathetic input to the heart can significantly increase both HR and contractile force up to 100%. Parasympathetic innervation, on the other hand, reduces HR and contractile force through nerve fibers predominantly supplying the atria. However, contractility can only be decreased to about 20%. Sympathetic enhancement of cardiac contractility is mediated by norepinephrine from the cardiac sympathetic nerves. Norepinephrine causes an increase in the shortening of the muscle fiber with a constant preload and total load, resulting in increased stroke volume. This effect is mediated by the stimulation of β -adrenergic receptors, mainly of the β_1 subtype (see Table 2) on the cardiac membranes, leading to an increase in cyclic AMP (cAMP). cAMP increases phosphorylase B activity, stimulating glycogen metabolism, and increasing energy supply for enhanced contractility. Combined with its effect on increasing HR, sympathetic stimulation can cause a two- to threefold increase in CO.

Calcium is necessary for effective contraction of cardiac muscle. Action potential causes release of calcium into the sarcoplasm of the muscle. Instantaneously, calcium ions diffuse into the myofibrils and catalyze the chemical reactions that promote sliding of actin and myosin filaments along one another, producing muscle contraction. Because muscle sarcoplasm does not have a large store of calcium, large amounts of extracellular calcium are needed to diffuse into the T-tubules, where they are bound to glycoproteins, and released as needed, to enhance contractility.

Heart Rate and Rhythm

Factors affecting HR do so by altering the electric properties of the cardiac pacemaker cells, which have an intrinsic rate and are age-dependent, being higher in infancy and diminishing with age. The autonomic nervous system has the most profound influence on HR. The sympathetic and parasympathetic systems act by changing the rate of spontaneous depolarization of the resting potential in the cardiac pacemaker cells. While sympathetic stimulation causes the HR to increase, parasympathetic stimulation causes it to fall. These reflexes are immediate and represent critical survival mechanisms. During periods of tachycardia, peak ejection velocity is increased. The net effect of the tachycardia is an increased CO. However, outside the normal adult physiologic range, large increases or decreases in HR result in a decrease in the net CO. In the adult, tachycardia of 170 bpm or greater allows too little time for ventricular filling. The small ejection volume cannot be overcome by the increased HR. Lower than normal HR, or bradycardia, causes a decreased CO because of a reduced stroke volume relative to the requirements of the individual. In the case of reduced HR below 40 bpm (in the adult), the increase in preload owing to increased filling time is limited because major ventricular filling, which occurs early in diastole, is not maintained for the duration of the diastolic period. CO decreases because stroke volume does not increase sufficiently.

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

<i>Drug name</i>	<i>Agonists</i>	<i>Antagonists</i>
Nonselective	Norepinephrine	Phentolamine
α_1	Cirazoline	Prazosin
α_{1A}	A61603 Oxmetazoline	(+) Niguldipine, 5-methyl urapidil, KMD-3213
α_{1B}		(+) -Cyclazosin
α_{1D}	BMY 7378	BMY-7378
α_2	UK14304	Idazoxan
		Rauwolscline
		Yohimbine
$\alpha_{2A/D}$	Oxymetazoline	BRL 44408
α_{2B}	Guanfacine	Imiloxan
α_{2C}		ARC 239
β -Adrenoceptor		
Nonselective	Isoproterenol	Propranolol
β_1	Xamoterol	Betaxolol Atenolol
β_2	Salmeterol Terbutaline	Butoxamine ICI 118,551
β_3	BR 37344 CL 316243	SR-59230A SR 58894
Dopamine receptor		
Nonselective	Dopamine	
D ₁ -like	Fenoldopam ^a	R(+)-SCH 23390 ^a
D ₁		
D ₅		
D ₂ -like	LY 171555	YM 09151
	SKF103376	Domperidone
D ₂	U91356A	L741,626
D ₃	PD128907	S(-)-Nafadotride
	R(+)-7-hydroxyPIPAT	U-99,194A
D ₄	PD168077	L-745, 870

^a Selective for D₁-like receptors but cannot distinguish between D₁ and D₅ receptors.
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HR is one of the most important determinants of myocardial energy consumption. Generally it is more energy efficient to increase CO by increasing stroke volume, rather than by increasing HR. Infants and children are more likely to increase their HR, and thus expend more energy in increasing their CO during stress.

Primary Regulation of Cardiac Output During Development

Effective circulation is necessary in very early embryonic development, and parallels structural development of the heart (4). As early as 5 wk postconception in humans, the basic circulatory parameter, HR, is present at about 100 bpm. CO is very dependent on HR and also on atrioventricular synchrony after formation of the four-chambered heart. Systolic function of the heart and, consequently CO, increases with gestational age. The EF of the embryonic ventricle is roughly 30–50%. The fetal heart has a limited ability to increase work following stretch, so the Frank-Starling curve is limited compared to adults. The lower wall stress in the embryo, owing to a smaller ventricular size and lower pressures, reduces the total afterload and enhances CO in the face of a high peripheral resistance. Afterload owing to wall stress increases as gestation progresses, reflecting the increase in ventricular size and transmural pressures while peripheral vascular resistance decreases.

Secondary Regulation of Cardiac Output

A variety of factors operate in the normal person to regulate CO over the long-term. These secondary control mechanisms do not have as great an influence on the heart as the components previously described. Secondary controls include cardiovascular reflexes and hormonal influences. Cardiopulmonary receptors, which are sensory nerve endings in the atria, ventricles, coronary vessels, and lungs, have chemo- and mechano-sensitive properties. The activity of these receptors is relayed to the nucleus of the tractus solitarius, via vagal afferents and spinal sympathetic afferent fibers. Stimulation of these receptors evokes responses similar to those noted with arterial baroreceptors. Thus, an increase in distension of the atria results in a decrease in circulating levels of vasopressin, aldosterone, and renin, among other hormones, but causes an increase in the natriuretic factors synthesized by the atrium and the ventricles (atrial natriuretic peptide, brain natriuretic peptide, C-type natriuretic peptide). Circulating atrial natriuretic peptide decreases with gestational and postnatal age (5). Depressor reflexes in the heart originating mainly from the inferoposterior wall of the left ventricle promote bradycardia, vasodilatation, and hypotension (Bezold–Jarisch reflex) (6). These are mediated by increased parasympathetic and decreased sympathetic activity. Left ventricular mechanoreceptor stimulation can also attenuate arterial baroreflex control of HR. Decreased activity of cardiac vagal afferents results in enhanced sympathetic activity and increased vascular resistance, renin release, and vasopressin secretion. Alterations in extracellular fluid volume influence CO via changes in venous return and BP. In fetal and newborn animals, however, cardiopulmonary receptors have minimal influence in the regulation of cardiovascular and autonomic responses to changes in BP or blood volume (7).

Peripheral Resistance

Blood flow through a vessel is determined by two primary factors: the amount of pressure forcing the blood through the vessel, and the resistance to flow. The resistance to flow in a blood vessel is best described as impedance because this takes into account inertial properties and viscosity of blood, elastic properties of blood vessels, and the variable geometries of blood

vessels during phasic flow. One of the most important factors influencing the flow through the arteries is the vessel diameter, since the conductance is proportional to the fourth power of the diameter. Therefore, flow is influenced more by changes in vascular resistance than by pressure changes. The variables influencing peripheral resistance are listed in Table 1.

Control Mechanisms for Blood Pressure Regulation

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

Arterial Baroreceptors

The degree of arteriolar constriction is determined by a balance between tonic output from the pressor areas of the cardiovascular center and the degree of inhibition from the baroreceptors. The arterial baroreceptors are the major fast-reacting, slowly adapting feedback elements to the central-neural cardiovascular regulatory system. Their function is to limit sudden changes in BP. Their mechano-sensitive nerve endings are located at the medial-adventitial border of blood vessels with elastic structure, mainly at the aortic arch and carotid sinuses. The receptors respond to deformation of the vessel in any direction, i.e., circumferential and longitudinal stretch. This results in the stimulation of mechano-sensitive channels that contain degenerative/epithelial sodium channel (DEG/ENaC) (8,9). The pressure diameter relationship is concave with the greatest distensibility at about 120–140 mmHg. There are two types of receptors in the carotid sinus: type I receptors are thin myelinated fibers; type II receptors are thick myelinated fibers with fine end branches terminating in neurofibrillar end plates. The latter receptors are also seen in the aortic arch.

An increase in BP stimulates the mechanosensitive receptors in the baroreceptors, inhibits the sympathetic nervous system, and activates the parasympathetic nervous system. This results in a decrease in HR, myocardial contractility, peripheral vascular resistance, and venous return. A decrease in BP decreases mechanosensitive stimulation of the baroreceptors, inhibits the parasympathetic nervous system, and activates the sympathetic nervous system. This results in an increase in HR, myocardial contractility, peripheral vascular resistance, and venous return (10). A second system, endogenous nitric oxide (NO), is involved in the short-term regulation of BP; increased arterial pressure increases shear stress, which leads to the generation of NO opposing the rise in BP by vasodilatation.

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

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

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

Nerve endings containing norepinephrine are found in the carotid sinus and aortic arch, and may influence the sensitivity of the sinus reflex. Norepinephrine given intravenously decreases distensibility of the sinus at low pressures, but increases distensibility at high pressure. In the conscious dog, sinus hypotension induces a reflex tachycardia and sympathetic vasoconstriction of the skeletal resistance vessels. The changes in the renal and mesenteric beds (45% of total peripheral resistance) seem to owe solely to autoregulation. In the anesthetized dog, sinus hypotension induces a greater magnitude and a more generalized pattern of sympathetic vasoconstriction, and may include both resistance and capacitance vessels. Several paracrine factors that affect the sensitivity of arterial baroreceptors have been reported, including prostanoids and NO. In general, vasoconstrictors decrease baroreceptor sensitivity while vasodilators increase baroreceptor sensitivity. However, NO decreases baroreceptor sensitivity independent of its vasodilator action. Reactive oxygen species (ROS) also decrease baroreceptor sensitivity, a mechanism that may contribute to the increase in systemic BP caused by ROS (11).

Adaptation of the Baroreceptors

The baroreceptors exert a tonic inhibitory influence on peripheral sympathetic activity. Baroreceptor nerves interact by mutual inhibitory addition; with a decrease in pressure, there is less reflex inhibition and a resultant increase in sympathetic outflow. While transient baroreceptor-induced changes in HR are primarily mediated by the parasympathetic nervous system, steady-state responses are owing to a greater involvement of the sympathetic nervous system. A sudden increase in pressure (with resultant stretching of the receptors) causes an immediate increase in baroreceptor firing rate. With continued elevation of the pressure, however, there is a decrease in the rate of baroreceptor firing. Initially the decrease is rapid, and during the succeeding hours and days it slows down. This adaptation, or resetting, in response to a lower or higher pressure seems to be complete in 2 d. This adaptation can occur at the receptor and nervous signal pathway (2). The resetting of the baroreflex is much more rapid in adults than in infants (12).

Arterial Baroreceptors During Development

Studies in humans and experimental animals suggest that arterial baroreceptors are present in the fetus and undergo postnatal maturation (12). There is an enhanced sensitivity of the efferent limb of the baroreflex in fetal life (12). In adults with intact arterial baroreceptors, a rapid head-up tilt is accompanied by an immediate increase in HR, and peripheral vascular resistance with maintenance of mean arterial pressure in the upper body. Several studies have suggested that in healthy preterm and term human infants, head-up tilting also increases HR in proportion to the degree of tilting. However, other studies have shown that in healthy preterm infants with a postconceptional age of 28–32 wk, a 45° head-up tilt results in an increase in peripheral resistance without any significant changes in HR (7). The increase in HR with a 45° head-up tilt increases with postconceptional age. In the conscious newborn dog, the magnitude of the increase in mean arterial pressure and peripheral resistance following bilateral carotid occlusion is less than in the adult. In addition, these changes occur without alterations in HR, similar to the effects noted in infants. In fetal sheep, only the increase in HR with a decrease in BP is noted. There is no relationship of arterial pressure and HR variability immediately after birth, but the fetal pattern resumes a few hours later (13).

Newborn lambs exhibit the classic inverse relationship between HR and BP, but the sensitivity is only about 50% that of an adult. The responses to small changes in BP is similar in fetal and newborn lambs. However, when the change in BP is greater than 15% the responses are different. In newborn lambs, a progressive tachycardia accompanies the increasing hypotension, owing to a combination of increased sympathetic outflow and parasympathetic withdrawal. There is no progressive tachycardia in the fetus; in fact, when the BP change is greater than 50%, bradycardia occurs, apparently due to augmentation of vagal parasympathetic tone.

There are age-dependent differences in the ability of the piglet to compensate for hemorrhage and hypoxia (14). Neonatal swine are better able to compensate for venous hemorrhage than for arterial hemorrhage (15). Volume expansion inhibits the sympathetic nervous system to a greater extent in older than in newborn lambs. Increasing arterial pressure by intravenous administration of vasoconstrictor agents results in smaller changes in HR in the newborn animal as well. Completion of sympathetic efferent pathways occurs before baroreceptor reflex activity is capable of modulating cardiac sympathetic activity. Therefore, maturation of baroreceptor reflex activity may be dependent on development of baroreceptor function, or of connections between baroreceptor and sympathetic efferents (12). The changes in baroreflexes during development are thought to be caused by afferent, central integration, and efferent pathways. The maturation of receptors for various humoral and hormonal agents (e.g., angiotensin II [ANG II], glucocorticoids, prostanoids, vasopressin) has been shown to affect baroreflex function.

Autonomic Regulation of Blood Pressure

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

CATECHOLAMINES

Epinephrine is released mainly from the adrenal medulla, while norepinephrine is released mainly in terminal nerve endings. In organs with dopaminergic nerves, a greater proportion of catecholamine released is dopamine. Norepinephrine synthesized at peripheral nerve endings is stored in subcellular granules. After a specific stimulus it is released into the synaptic cleft, where it interacts with specific receptors presynaptically and at the effector cell. The neurotransmitter is inactivated to a large extent by reuptake into the storage granules. This reuptake process (reuptake-1) is stereoselective, sodium-dependent, and of high affinity. A presynaptic reuptake that is of low affinity and nonsodium-dependent has been termed reuptake-2. There are specific amine transporters. Although the enzymatic degradation of the neurotransmitter by monoamine oxidase and catechol-*O*-methyl transferase is much less important in termination of neurotransmitter action in nervous tissue, this metabolism plays an important role in vascular smooth muscles (16). The remainder of the neurotransmitter which escapes reuptake-1 and -2 is released into the circulation. Since only about 20% of the total appears in the circulating pool, the plasma levels of catecholamines are merely a rough index of adrenergic activity.

ADRENERGIC AND DOPAMINERGIC RECEPTORS

For the neurotransmitter to exert its specific effect, it must occupy a specific receptor on the cell surface. Catecholamines can occupy specific pre- and postsynaptic receptors. Each receptor has different subtypes (17–19). Table 2 lists some drugs that have relative selectivity for each particular receptor subtype in the peripheral vascular bed. Occupation of presynaptic α_2 -adrenergic and S_2 -like dopamine receptors inhibits norepinephrine release. Occupation of presynaptic β_2 -receptors enhances norepinephrine release. At low levels of nerve stimulation, norepinephrine release is increased; at high levels of stimulation, the inhibitory effects of presynaptic α_2 -adrenergic receptors predominate, acting as a short-loop feedback. The antihypertensive effects of dopamine agonists and (β -adrenergic antagonists) may owe in part to their ability to decrease release of norepinephrine at the terminal nerve endings.

α_1 -ADRENERGIC RECEPTORS

Three α_1 -adrenergic receptors are expressed in mammals, α_{1A} (originally designated as the α_{1C} when cloned), α_{1B} , and α_{1D} . Vascular bed may impart receptor subtype specificity. Thus, α_{1A} may mediate contraction of renal and caudal arteries, whereas α_{1D} -adrenergic receptors may regulate the contraction of the aorta, femoral, iliac, and superior mesenteric arteries. Mice deficient for the α_{1A} -adrenergic receptor have decreased BP, as do mice deficient for the α_{1D} -adrenergic receptor (20). The α_{1D} -receptor-deficient mice are resistant to the hypertensive effects of sodium chloride. In contrast, α_{1B} -adrenergic receptors may not regulate vascular smooth muscle contraction. Mice deficient for these receptors have normal BP in the basal state. Pharmacological evidence for this has been shown in studies of mice deficient for a specific α_1 -adrenergic receptor subtype (21,22). Hypertrophy in neonatal cardiac myocytes is mediated primarily by the α_{1A} - and α_{1B} -adrenergic receptors. Aortic hypertrophy, on the other hand, is primarily owing to the actions of the α_{1D} -adrenergic receptors.

α_2 -ADRENERGIC RECEPTORS

There are three α_2 -adrenergic receptor subtypes, $\alpha_{2A/D}$, α_{2B} , and α_{2C} . The α_{2A} class predominates, and these receptors decrease BP and mediate most of the classical effects of α_2 -adrenergic stimulation. In contrast, α_B -adrenergic receptors, predominantly found outside of the

central nervous system at extrajunctional or postsynaptic sites, produce vasoconstriction and thus counteract the hypotensive effects of α_{2A} -adrenergic receptor stimulation. α_{2C} -adrenergic receptors do not have cardiovascular effects but may mediate the hypothermic response (23).

β -ADRENERGIC RECEPTORS

Disruption of either the β_1 , β_2 -adrenergic receptor, or both, does not affect HR or resting BP in mice. Mice lacking the β_1 -adrenergic receptor are unresponsive to cardiac β -adrenergic receptor stimulation, suggesting that neither β_2 - nor β_3 -adrenergic receptors play a role in the inotropic or chronotropic responses in the mouse (24), and indeed, the effect of the non- β -adrenergic subtype receptor agonist isoproterenol is not altered in β_2 -adrenergic-receptor null mice. However, the hypotensive response to isoproterenol is impaired in both β_1 or β_2 -adrenergic null mice (25,26). β_3 -adrenergic receptors do not have major effects on the cardiovascular system (27).

DOPAMINE RECEPTORS

Dopamine is an important regulator of BP. Presynaptic/junctional and postsynaptic/junctional, or extrasynaptic dopamine receptors, are found in many organs and vascular beds. Dopamine receptors have also been described in the heart, but their function remains to be determined (28,29). Dopamine's actions on renal hemodynamics, epithelial transport, and humoral agents such as aldosterone, catecholamines, endothelin, prolactin, pro-opiomelanocortin, renin, and vasopressin place it in a central homeostatic position for the regulation of extracellular fluid volume and BP. Dopamine also modulates fluid and sodium intake via its actions in the central nervous system (CNS) and gastrointestinal (GI) tract, and by regulation of cardiovascular centers that control the functions of the heart, arteries, and veins. Abnormalities in dopamine production and receptor function accompany a high percentage of human essential hypertension and several forms of rodent genetic hypertension. Dopamine receptor genes, as well as genes encoding their regulators, are in loci that have been linked to hypertension in humans and in rodents. Moreover, allelic variants (single nucleotide polymorphisms [SNPs]) of genes that encode the regulators of the dopamine receptors, alone or in combination with variants of genes that encode proteins that regulate the renin-angiotensin system (RAS), are associated with human essential hypertension.

Each of the five dopamine receptor subtypes (D_1 , D_2 , D_3 , D_4 , and D_5) participates in the regulation of blood pressure by mechanisms specific to the subtype. Some receptors (D_2 and D_5) influence the central and/or peripheral nervous system; others influence epithelial transport (30–33). Both the D_1 -like dopamine receptors (D_1 and D_5) and the D_3 receptor decrease epithelial sodium transport (30,31). D_4 receptors inhibit the effects of aldosterone and vasopressin in the renal cortical collecting duct (32,33). D_2 -like receptors, under certain circumstances, may increase sodium transport (34,35). Dopamine can regulate the secretion and receptors of several humoral agents (e.g., the D_1 , D_3 , and D_4 receptors interact with the RAS). The D_1 -like receptors are vasodilatory while the D_2 -like receptors can mediate vasodilation or vasoconstriction depending upon the starting vascular resistance. When vascular resistance is high, D_2 -like receptors are vasodilatory by inhibition of norepinephrine release. However, when vascular resistance is low, D_2 -like receptors mediate vasoconstriction probably via the D_3 receptor (34). Modifications of the usual actions of the receptor can produce blood pressure changes. In addition, abnormal functioning of these dopamine receptor subtypes impairs their antioxidant function (36).

SIGNAL TRANSDUCTION

The signal resulting from occupation of cell membrane receptors is amplified by the intervention of other agents called second messengers. Occupation of either β -adrenergic receptor subtype or the D_1 -like class of dopamine receptor by agonists stimulates adenylyl cyclases; agonist occupancy of α_2 -adrenergic receptors, or dopamine D_2 receptors, leads to inhibition of adenylyl cyclases. The changes in intracellular cyclic adenosine monophosphate levels alter the activities of certain enzymes, e.g., protein kinase A, and mediate the eventual response of the effector cell. Certain drugs (e.g., nitrites) exert their vasodilatory effect by stimulation of guanylate cyclase activity (37). Another second messenger is associated with the phosphoinositide system. The α_1 -adrenergic and the D_1 dopamine receptors are linked to phospholipase C; stimulation leads to an increase in formation of inositol phosphates and diacylglycerol. Inositol phosphates increase intracellular calcium, whereas diacylglycerol stimulates protein kinase C. Occupation of α_1 -adrenergic and D_1 dopamine receptors may also result in the activation of phospholipase A_2 , increasing the formation of biologically active arachidonate metabolites by the action of cyclooxygenases (prostaglandins, thromboxanes), lipoxygenases (leukotrienes), and cytochrome p450 monooxygenase (e.g., 20 hydroxyeicosanotetraenoic acid).

RECEPTOR REGULATION

Signal transduction involves “on” and “off” pathways to ensure that signaling is achieved in a precisely regulated manner (38–40). One “off” pathway is receptor desensitization, or loss of receptor responsiveness. Receptor desensitization is a mechanism to dampen short-term agonist effects following repeated agonist exposure. Desensitization involves several processes, including phosphorylation, sequestration/internalization, and degradation of receptor protein (38–40). An initial step in the desensitization process is the phosphorylation of the receptor by a member or members of the G protein-coupled receptor kinases (GRKs) family. GRKs are serine and threonine kinases that phosphorylate G protein-coupled receptors (GPCRs) in response to agonist stimulation. The phosphorylation of GPCRs, including D_1 receptors, leads to the binding of a member or members of the arrestin family, an uncoupling of the receptor from its G protein complex, and a decrease in functional response (38–41). The phosphorylated GPCR and arrestin complex undergo internalization via clathrin-coated pits into an endosome where the GPCR is dephosphorylated (38–40), facilitated by protein phosphatases (42), and recycled back to the plasma membrane, or degraded by lysosomes and/or proteasomes. These processes may be specific to a particular receptor.

DEVELOPMENT OF RECEPTOR REGULATION

There are developmental changes in the desensitization process. The neonatal rat heart is resistant to β -adrenergic receptor desensitization (43). Rather, β -adrenergic agonists produce sensitization caused by the induction of adenylyl cyclase activity, as a consequence of loss of $G\alpha_i$ protein and function, enhancement of membranous expression of $G\alpha_s$, and, in particular, the shorter but more active 45 kDa $G\alpha_s$. The role of $G\beta/\gamma$ was not determined but in the kidney we found that the decreased inhibitory effect of D_1 receptors on the sodium hydrogen exchanger type 3 is caused by increased expression and linkage of the G protein subunit $G\beta/\gamma$ (44).

CATECHOLAMINES AND OTHER VASOACTIVE AGENTS

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

ADRENERGIC SYSTEM DURING DEVELOPMENT

The low systolic BP at birth, owing to low CO and peripheral resistance, increases rapidly in the first 6 wk of life, remains at a constant level until age 6, and increases gradually until age 18 yr. The pattern is similar for diastolic BP, except that there is a slight decrease in diastolic BP in the first 6 mo of life (relative to the BP in the first week of life). The increase in BP with age in preterm infants occurs as a function of postconceptional age. With advanced age (>60 yr), systolic BP continues to increase. Diastolic BP declines somewhat, leading to an increase in pulse pressure. Increased pulse pressure has been thought to play an independent role in the pathogenesis of the complications of high BP (45). The increase in BP accompanying age is owing to a rise in both CO and total peripheral resistance. The age-related changes in vascular resistance are selective, because in the perinatal period there is a rapid fall in resistance in the lungs, small intestines, brain, and kidney while resistance increases in the femoral vessels (46). The increase in femoral resistance accompanying age is most likely related to an increase in vascular reactivity to vasoconstrictors, with no differential effects of vasodilators (NO and bradykinin). The decrease in regional vascular resistance may be caused by an increase in vessel growth, and changing sensitivities and reactivities to vasoconstrictor and vasodilator agents. The increase in regional blood flow accompanying age cannot be accounted for by an increase in BP. Indeed, in the immediate perinatal period, the increase in regional blood flow with postnatal age is independent of BP (47). In the first 6 mo of life, systolic BP increases, but diastolic BP actually decreases after the first 2 wk of life. This transient decrease in diastolic BP in the first few months of life is associated with a low intestinal vascular resistance (48). This is apparently mediated by NO. Interestingly, increased NO production in the neonatal renal arterial bed (49,50a) also dampens the increased vasoconstriction afforded by ANG II early in perinatal life, and catecholamines later in prenatal life (51). NO however, does not play an important role in cerebrovascular responses in the newborn.

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

Study of the role of the adrenergic nervous system in the control of cardiovascular dynamics is complicated by species differences. Some studies have suggested that pigs and dogs provide the closest model to the newborn human in terms of cardiovascular development (52,53). On the other hand, the sheep fetus is a very useful model for chronic-conscious studies (12,54).

DEVELOPMENT OF THE SYMPATHETIC NERVOUS SYSTEM

The development of the sympathetic nervous system can be divided into three stages (55). In the first stage, the neural crest cells migrate to their positions within the body tissues. In the second stage, the cell number and type is refined by cell death (apoptosis). The third stage is concerned with the maturation of synaptic connections and selection of the neurotransmitter. Cholinergic development generally takes place prior to adrenergic differentiation; however, transition from adrenergic to cholinergic function can also occur. In the neonatal rat heart, perinatal β -adrenergics positively regulate the development of sympathetic innervation and suppress the development of m_2 muscarinic acetyl choline receptors (56). A critical event in the development of the adrenergic nervous system is the establishment of functional innervation of the different organs. Function requires that central nervous pathways to the preganglionic neurons be established, that information be relayed to postganglionic neurons, and that neurotransmitter synthesis, release, and reuptake, and postreceptor mechanisms be operative. Effector organ innervation involves the outgrowth of new axons, appearance of intense fluorescence, and differentiation of adrenergic nerve varicosities. Maturation of the nerve-terminal-effector complex occurs before ganglionic transmission is fully developed and is largely independent of neural connections. In the heart, the development of β -adrenergic receptors and their responsiveness to catecholamines is not closely linked to innervation. Nonsympathetic hormonal factors appear to control early maturation of receptors and the growth and development of the nervous system.

PLASMA CATECHOLAMINES

Plasma norepinephrine and dopamine levels decrease gradually with the advance of gestational weeks (57). Birth is associated with an increase in circulating catecholamines. Umbilical arterial epinephrine and norepinephrine concentrations in infants delivered vaginally are greater than those in infants delivered by cesarean section (58–60). Because there are some studies showing no difference in plasma concentrations between infants delivered vaginally and those by cesarean section (61,62), stress *per se* may not be responsible for the high catecholamine levels with vaginal delivery. Studies in the fetal sheep indicate a surge in plasma catecholamines with the onset of parturition that is accentuated by cord-cutting (63). The half-life of circulating catecholamines in the preterm infant may be longer than in older children, owing in part to lower levels of catecholamine-degrading enzymes. However, children may metabolize catecholamines more rapidly than adults. Preterm infants have greater levels of epinephrine in umbilical arterial plasma than full-term human infants. Preterm fetal sheep also have higher circulating catecholamine levels than their full-term counterparts. The circulating levels of catecholamines decrease with maturation, but beyond 20 yr of age plasma norepinephrine increases. Adrenal medullary activity is lower than adrenergic nervous activity at birth and increases with maturation.

URINARY CATECHOLAMINES

Urinary catecholamines are low at birth and increase with gestational and postnatal age (64–66). Small-for-gestational-age babies have greater sympathoadrenal activity than babies of the same gestational age (64). Newborn preterm infants excrete less norepinephrine and more dopamine than term infants, and epinephrine excretion is comparable. At 2 wk of age, urinary dopamine and metabolites are greatly increased in preterm infants. Beyond 1 yr of life, the developmental patterns of adrenergic nervous and adrenal medullary activity are similar, and reach

mature values at 5 yr of age. When expressed as a function of surface area or weight, no changes in urinary catecholamines and metabolites occur after 1 yr of age. In the first 5 yr of life, however, sympathoadrenal activity is less in girls than in boys. It should be kept in mind, though, that circulating and urinary levels of catecholamines are only rough indices of adrenergic activity.

CATECHOLAMINES AND ADAPTATION TO EXTRAUTERINE LIFE

Catecholamine secretion at birth may be important in the adaptation of the fetus to extrauterine life (63,67). Complete ganglionic blockade before delivery of the lamb does not attenuate the normal postnatal rise in BP, indicating that the autonomic nervous system may not play a significant role in the increase in systemic pressure after birth. However, although clamping of adrenal vessels did not alter mean BP of very young puppies (68), in the newborn dog adrenalectomy leads to hypotension and bradycardia. In addition, adrenergic blockade in the newborn lamb reduces systemic pressure whereas no effect is seen in adult sheep. More evidence of the importance of the adrenergic nervous system during the neonatal period includes impaired myocardial contractile responses to adrenergic agents and hypoxia following adrenalectomy.

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

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

REGIONAL VASCULAR FLOW AND RESISTANCE DURING DEVELOPMENT

The development of renal and intestinal circulation is discussed in some detail because splanchnic vascular resistance contributes significantly to peripheral vascular resistance. β -adrenergic relaxation of the aorta of rabbits increases with age, reaching a maximal level at 1 mo; thereafter a decline in responsiveness occurs. In dogs, stimulation of lumbar sympathetics induces femoral vasodilatation early in life; after 2 mo a greater vasoconstriction is noted. This corresponds to a marked increase in adrenergic innervation. In the piglet, the renal vascular

response to β -adrenergic stimulation is also less in the immediate newborn period compared to adults but may be markedly increased some time before maturation (68). These changes in renal β -adrenergic responsiveness have been correlated with β -adrenergic receptor density in the dog (69). However, β_2 -adrenergic vasodilatory effects are enhanced in the renal vascular bed of the fetal lamb (70).

The maturation of blood vessel reactivity to α -adrenergic stimulation is regional bed-dependent. In general, the response of the canine aorta and sheep carotid to norepinephrine is less pronounced in the newborn than in the adult. This occurs in spite of comparable responsiveness to KCl (71). The vasoconstrictor effects of α -adrenergic drugs are also less pronounced in immature than in mature animals. In the neonatal rat femoral artery, norepinephrine causes a vasodilation, not vasoconstriction, an effect that is mediated by NO (72). In baboons, the maximum vasoconstrictor response to norepinephrine, thromboxane mimetic, and potassium increased with gestational age but the sensitivity to these vasoconstrictors was similar (46).

RENAL VASCULAR BED

Renal blood flow increases progressively with conceptional age, reaching term values by about 35 wk postconception. Forty weeks postconception, renal blood flow, expressed as a function of surface area, increases with postnatal age, reaching middle-age adult values by 1–2 yr of life. The increase in renal blood flow is associated with a fall in renal vascular resistance. Color Doppler ultrasonography has been used to determine renal resistive index, which correlates with renal vascular resistance. In general, the values obtained using clearance methods (e.g., para-aminohippurate) have correlated well by the renal resistive index (73). The increase in renal blood flow associated with age is due to renal growth, an increase in BP, and a decrease in renal vascular resistance. The high renal vascular resistance in the perinatal period has been shown to be caused by alterations in renal vascular smooth muscle reactivity, and sensitivity to vasodilators and vasoconstrictors. After the immediate newborn period, the neonatal renal and cerebral circulation is more sensitive to α -adrenergic stimulation in dogs, pigs, guinea pigs, and baboons (51,74,75). The isolated renal vessels of fetal lamb studied in vitro and in vivo are also more reactive to α -adrenergic stimulation than their newborn or adult counterparts (76). The increased renal α_1 - and α_2 -adrenergic effects in fetal sheep are related to increased α -adrenergic receptor density. Competition experiments and rank adrenergic antagonist potency suggested the presence of only the α_{1B} -adrenergic receptor in fetal and adult sheep kidneys. However, the α_{1B} -adrenergic receptor does not mediate vasoconstriction in adults. The α_2 -adrenergic receptor that was found only in the fetal sheep studied had a low affinity to rauwolscine, which is unlike that described in most species for α_2 -adrenergic receptors (77). The molecular biological class of these receptors during development has not been studied.

Inherent renal vascular hypersensitivity or hyperreactivity may be masked by counter-regulatory vasodilator mechanisms. In the fetal sheep studied, renal vascular β_2 -adrenergic receptor-mediated renal vasodilatory capacity is enhanced during fetal life (78). Cerebral arteries from premature and newborn baboons showed a more marked relaxation response to isoproterenol than did arteries from adult animals (74). In the piglet, the renal vasoconstrictor effects of ANG II are counteracted by the vasodilatory action of NO (49,50,79). However, the contribution of specific adrenergic receptors and regulation of NO level or availability to the development of renal circulation remains to be determined.

The neonatal renal circulation is also more responsive to the effects of renal nerve stimulation in some species (80). While renal nerve transection in piglets leads to an increase in renal

blood flow (80), this effect is not seen in fetal sheep. Moreover, renal nerve stimulation during α -adrenergic blockade actually increases renal blood flow (70). In the neonatal dog kidney, increased α -adrenergic effects are related to increased α -adrenergic receptor density (69). Dopamine mainly induces a vasoconstrictor response (an α -adrenergic receptor effect) in the early neonatal period (69). Even low dosages, which produce renal vasodilatation in the adult kidney, are associated with renal vasoconstriction in the newborn period. The vasodilator effects of dopamine become evident in the femoral circulation before being noted in the kidney. When α - and β -adrenergic receptors are blocked during dopamine infusion, the renal vasodilator effect of dopamine is still less pronounced in the fetus and the newborn animal than in the adult. In contrast to the correlation between renal vascular responses and α - and β -adrenergic receptor density, no correlation is observed with dopamine receptors and the age-related changes in renal dopamine responsiveness.

The low renal blood flow in the young is due to several factors, including smaller size, decreased number of glomeruli, lower systemic pressure, and higher renal vascular resistance. The increased renal vascular resistance in the newborn is most likely due to increased activity of the RAS, as well as to increased sensitivity to vasoconstrictor catecholamines, itself a product of receptor and postadrenergic receptor mechanisms. Critical vasodilators, such as NO, may act to counterbalance these vasoconstrictor forces. The increase in renal blood flow associated with age presumably occurs, in part, as the vasoconstrictor influences decline.

INTESTINAL VASCULAR BED

Intestinal blood flow, like renal blood flow, increases with gestational age, postconceptional age, and maturation (81). Fetal intestinal vascular resistance is high during fetal life. In the piglet, there is a decrease in intestinal vascular resistance in the first few days of life, only to progressively increase after the first week of life. This is in contrast with kidneys, which exhibit a progressive decrease in renal vascular resistance in the perinatal period. The neonatal intestinal circulation is controlled by inherent myogenic response and NO similar to that seen in the neonatal renal circulation. Like the neonatal kidney neonatal intestinal circulation may also be regulated by alterations in α -adrenergic receptor (82). However, in contrast to the neonatal kidney, endothelin plays a part in the regulation of neonatal intestinal circulation. In older piglets, regulation of the intestinal circulation does not involve NO or endothelin, the responses being mostly passive in nature (48,83). In contrast to the importance of NO in the renal and intestinal vasodilator response in the newborn, bradykinin and prostanoids perform this role in the neonatal cerebral vascular bed (84). However, with maturation NO assumes a more important role.

CONCLUSION

Increases in BP with age in the first few months of life are mainly owing to increases in CO. Vascular resistance in many vascular beds may transiently decrease because of increased production of, or the availability of, NO, or prostanoids. Increased sensitivity to β -adrenergic stimulation may also play a role. The involvement of a particular agent is regional bed dependent. While the maturation of receptor classes involved in the regulation of CO and vascular resistance is known, the maturation of specific receptor subtypes in different vascular beds remains to be determined.

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