5.13 Regulation of Arterial Pressure

Learning Objectives

- Explain why arterial pressure both drives and derives from flow
- Describe what is meant by the term "baroreceptor"
- Describe the anatomic location of the cardiac baroreceptors
- Describe the response of the baroreceptors to arterial pressure
- Explain the reflex effect of raising blood pressure on parasympathetic and sympathetic input to the heart and vasculature
- Explain the reflex effect of lowering blood pressure on parsympathetic and sympathetic input to the heart and vasculature
- Identify the main regions of the brain involved in the baroreflex
- Describe the respiratory sinus arrhythmia and explain its origin
- Recognize and describe the individual block components of the renal–cardiovascular systems diagram
- List the major hormonal influences on long-term regulation of blood pressure
- Describe the effect of ADH, RAA, and ADH on the renal function curve

ARTERIAL PRESSURE *DRIVES* FLOW BUT ARTERIAL PRESSURE ALSO *ARISES* FROM FLOW

The first law of the cardiovascular system, which we have used repeatedly, is written as

$$[5.13.1] \qquad Q_V = \frac{\Delta P}{R} \qquad CO = \frac{P_A - P_{RA}}{TPR}$$

where Q_V is the flow around the entire circulatory loop, equal to the cardiac output, CO, P_A is the pressure in the arteries, specifically in the aorta, P_{RA} is the pressure in the right atrium, and TPR is the total peripheral resistance. Generally the pressure in the right atrium is very small compared to the arterial pressure, and this equation can be approximated as

$$[5.13.2] \qquad P_A = CO \times TPR$$

This is an empirical relationship, not a causal one. For example, this equation indicates that decreasing the TPR by a factor of 2 will halve the arterial pressure *if* CO is maintained constant. Although this is true, decreasing the TPR by a factor of 2 generally will increase cardiac output (see Chapter 5.12).

The arterial pressure is pulsatile. The proper pressure to use in Eqns [5.13.1] and [5.13.2] is the **mean arterial pressure**, which is typically approximated as the diastolic pressure plus one-third of the pulse pressure (Eqn [5.9.9]). The actual mean arterial pressure depends on the systole duty cycle, the fraction of time the heart spends in systole, which varies with heart rate. A more recent study (Razminia et al., Validation of a new formula for mean arterial pressure calculation. Catheterization and Cardiac Interventions, **63**:419–425, 2004) suggests that we use the equation

$$[5.13.3] \qquad P_A = P_{diastolic} + (0.33 + 0.0012 \times HR)\Delta P_{pulse}$$

which corrects for the changes in the duty cycle of the heart with the heart rate. Here P_A is the mean arterial pressure, $P_{diastolic}$ is the diastolic pressure, HR is the heart rate, and ΔP_{pulse} is the pulse pressure.

Although Eqn [5.13.1] is consistent with our idea that pressure drives flow, pressure within the arteries is also generated by flow. Consider the experiment in Chapter 5.12 in which we imagined that we drained the circulatory system of blood completely, and then began to fill it up again. When we add enough blood to make the pressure everywhere equal to zero, we have added the **unstressed volume**. On adding more volume, the pressure increases linearly with the added volume. The volume above the unstressed volume is the **stressed volume**. The stressed volume of blood distributes itself between the venous and arterial compartments. Since the venous compliance is much larger than the arterial compliance, most of the stressed volume is in the veins. We can calculate the fraction of volume in each compartment. We define three compliances: one for the venous side, C_V, one for the arterial side, C_A, and one equivalent compliance for the entire system, C_S:

$$[5.13.4a] \qquad C_S = \frac{\Delta V_S}{\Delta P_S}$$

$$[5.13.4b] \qquad C_V = \frac{\Delta V_V}{\Delta P_V}$$

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[5.13.4c] $$C_A = \frac{\Delta V_A}{\Delta P_A}$$

Since the pressure is the same everywhere, we can write

[5.13.5] $$\Delta P_V = \Delta P_A = \Delta P_S = \frac{\Delta V_S}{C_S}$$

Inserting this back into Eqns [5.13.4b] and [5.13.4c] and rearranging for the volume increments, we get

[5.13.6] $$\Delta V_V = \frac{C_V}{C_A + C_V}\Delta V_S$$
$$\Delta V_A = \frac{C_A}{C_A + C_V}\Delta V_S$$

This makes use of Eqn [5.12.5], which states that the compliance of the system is the sum of the compliances. Thus, the volumes in the venous and arterial side distribute themselves according to their relative compliances. The ratio of the venous compliance to the arterial compliance has been estimated in experimental animals to be about 18:1, so that $C_V/(C_V + C_A) \approx 18/19$ and $C_A/(C_V + C_A) \approx 1/19$. Thus, most of the stressed volume is in the venous side of the circulation. We can estimate the individual compliances from the slope of the line in Figure 5.12.4. When withdrawing or adding blood, mean systemic pressure increases according to Eqns [5.13.4a,b,c] with the compliance of the entire system. The slope is about 7 mmHg L^{-1}. This is the inverse of C_S. Thus we have two equations in two unknowns:

[5.13.7] $$C_S = C_V + C_A \approx 0.142 \text{ L mmHg}^{-1}$$
$$C_V \approx 18 \times C_A$$

Solving for C_A and C_V, we find $C_A \approx 0.007$ L mmHg^{-1} and $C_V \approx 0.135$ L mmHg^{-1}.

Suppose now that we have added back the original blood volume. The pressure in the system, with the heart stopped, is the **mean systemic pressure**. Most of the blood will be in the venous system because it has the larger volume and the larger compliance. Now suppose we start up the heart. As in our analysis in Chapter 5.12, removing a volume ΔV_{SV} from the venous compartment to the arterial compartment will raise the arterial pressure and lower the venous pressure. For a typical stroke volume of about 70 mL, the pressure increases by $\Delta V_{SV}/C_A$ in the arteries and decreases by $\Delta V_{SV}/C_V$ in the veins. Using the approximate values for C_A and C_V that we calculated above, this increases P_A by 10 mmHg and decreases P_V by 0.5 mmHg. A single heart beat does not move enough blood to set the normal arterial pressure. Repetitive heart beats continue to move blood from the venous to the arterial side of the circulation. If compliance is independent of volume, then a mean arterial pressure would obtain when about 650 mL of blood was removed from the venous side to the arterial side (93 mmHg $\times$ 0.007 mL mmHg^{-1} = 651 mL). This would lower the venous pressure from 7 mm Hg mean systemic pressure to about 2.2 mmHg. Thus, the operating pressures in the arterial side and venous side require about nine stroke volumes. The heart actually pumps more than that to achieve the shift in volume, because part of the transferred volume returns to the venous side while the heart makes the transfer. So if we were to start the heart up again when the blood is evenly distributed so that the pressure is the mean systemic pressure everywhere, it would take more than nine heart beats to reach normal pressure.

This purpose of this calculation is to emphasize that **the heart produces arterial pressure**. The pulsatile pressure of the left ventricle is translated to the sustained pressure of the vasculature by the elasticity or compliance of the vessels.

REGULATION OF ARTERIAL PRESSURE OCCURS ON THREE SEPARATE TIMESCALES INVOLVING THREE DISTINCT TYPES OF MECHANISMS

As pointed out above, the heart causes the high arterial pressure by pumping blood from the low-pressure, venous side of the circulation to the high-pressure, arterial side. The pressure that results could be increased by increasing the stroke volume of the heart, by changing the compliance of the arterial system or its resistance to run off of the stroke volume placed in it by the heart, or by changing the volume of blood in the vasculature. These three distinct mechanisms of regulating the arterial pressure are controlled by three separate and distinct parts of the cardiovascular system. Thus arterial pressure is regulated by controlling three fundamental and independent variables:

1. **Cardiac contractility** (control of the heart's strength of contraction)
2. **Vascular smooth muscle contractility** (caliber and compliance of the vessels)
3. **Blood volume** (regulation of renal function).

The mechanisms involve:

- **Neurogenic mechanisms:** fast response (seconds)
- **Hormonal mechanism:** intermediate response (minutes to hours)
- **Intrinsic mechanisms**: slow response of blood volume (days to weeks).

BARORECEPTORS IN THE CAROTID SINUS AND AORTIC ARCH SENSE BLOOD PRESSURE

Sensors for the arterial pressure are called **baroreceptors**, but these actually sense stretch. Baroreceptors are found in the **carotid sinus** and the **aortic arch** (see Figure 5.13.1). The carotid sinus is a thin-walled dilatation located at the proximal end of the internal carotid artery just above the bifurcation of the common carotid artery into the internal and external carotid artery. Increasing pressure in the internal carotid stretches the walls of the carotid sinus, which excites the baroreceptors and increases their firing rate.

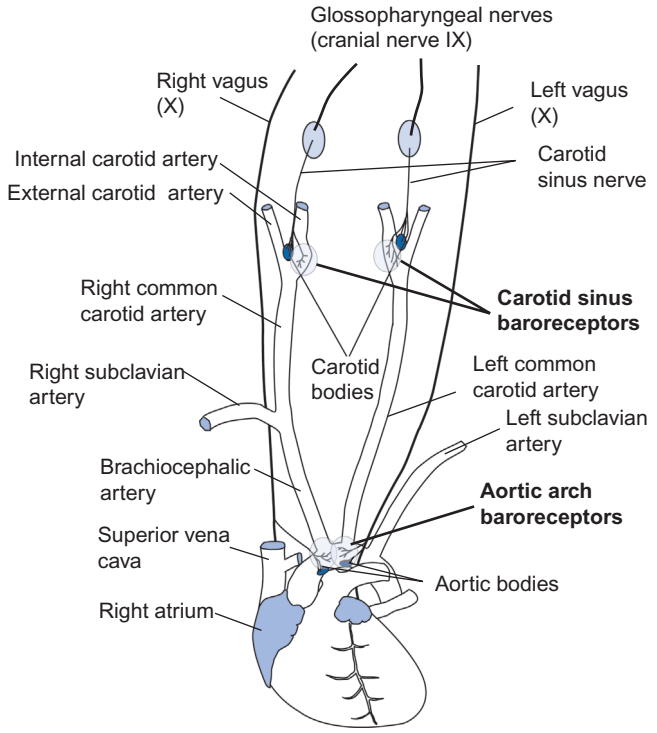

FIGURE 5.13.1 Location of the arterial baroreceptors. Stretch receptors that sense arterial pressure are located in the carotid sinus, near the bifurcation of the common carotid artery form that is the internal and external carotid arteries, and in the aortic arch. Stretch of these vessels excites baroreceptor afferents. The afferents from the carotid bodies travel to the central nervous system over the glossopharyngeal nerve. Afferents from the aortic arch reach the CNS over the vagus nerve.

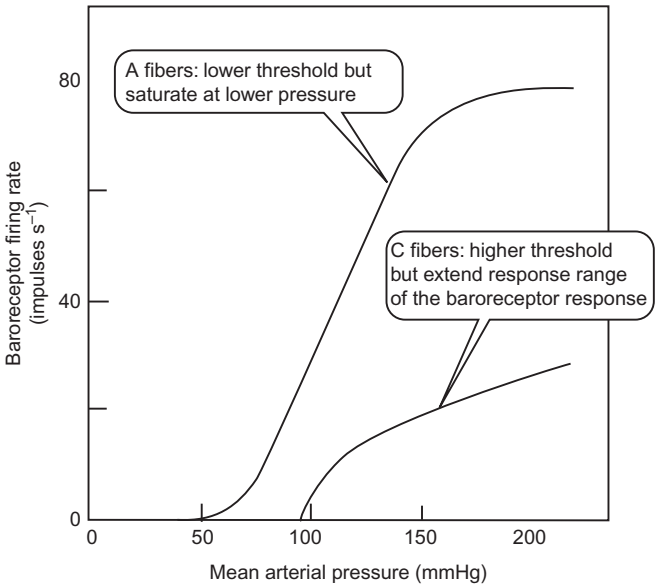

FIGURE 5.13.2 Heterogeneity of baroreceptor responses. Type A fibers are myelinated fibers that respond to low pressures but saturate first at pressures around 150 mmHg. C fibers have higher thresholds, between 70 and 140 mmHg, but continue to respond at higher pressures. (Source: *Adapted from H.M. Coleridge, J.C.G. Coleridge, and H.D. Schultz,* Journal of Physiology ***394****:2910—313, 1987.*)

Large diameter, myelinated **baroreceptor A fibers** activate at blood pressure between 30 and 90 mmHg. Therefore, they are active at normal blood pressure levels but become saturated with higher blood pressure and therefore cannot inform the CNS about high blood pressure.

Unmyelinated **baroreceptor C fibers** are more numerous than the A fibers. They have lower conduction velocities, but higher thresholds, in the range of 70−140 mmHg. At normal blood pressure, only about a quarter of the C fibers are activated. At progressively higher pressures, progressively more C fibers are recruited (see Figure 5.13.2).

The rate of firing of the baroreceptors responds not only to stretch but the rate of stretch. Thus, a rapid rise in blood pressure elicits a burst of impulses that subsequently slows. The rapid burst of impulses is called the **dynamic** response. The slower, steady response to static stretch corresponds to the **static** response. This phenomenon is illustrated in Figure 5.13.3.

As blood pressure increases in the range of normal, the rate of firing of individual baroreceptor A fibers increases, but additional baroreceptor C fibers begin firing as the pressure exceeds their threshold. This is called recruitment. Both the carotid sinus nerve and aortic nerves contain a large number of fibers. Because of the different thresholds, the aggregate response of the afferent nerves has a greater usable range than the response of any one fiber or of any one type of fiber.

As P_A increases, the aggregate afferent impulses from the baroreceptors will increase, with greater proportions from the C fibers as the pressure increases. When the pulse pressure increases, the incremental burst of activity during systole is roughly proportional to the pulse pressure. The ability to sense the size of the pulse is important whenever the stroke volume decreases, such as in **orthostasis** (adoption of an upright posture) and in moderate **hemorrhage**, when the stroke volume falls without much change in mean arterial pressure (see Figure 5.13.4).

THE BAROREFLEX REGULATES HEART AND VASCULATURE TO STABILIZE BLOOD PRESSURE

Increases in blood pressure increase the baroreceptor input to the brain stem through the glossopharyngeal and vagus nerves. The brain stem integrates this information, subsequently reducing sympathetic outflow to the cardiovascular system and increasing parasympathetic outflow over the vagi to the heart. The effects include:

- Decreased heart rate due to increased parasympathetic stimulation of the SA node. Together with reduced sympathetic activity, the result is **bradycardia** and **reduced myocardial contractility**. These reduce cardiac output.
- Reduced sympathetic output to the vasculature causes vasodilation and therefore a **fall in total peripheral resistance (TPR)**.

Since Eqn [5.13.2] tells us that the average arterial pressure is CO × TPR, and the baroreflex reduces both

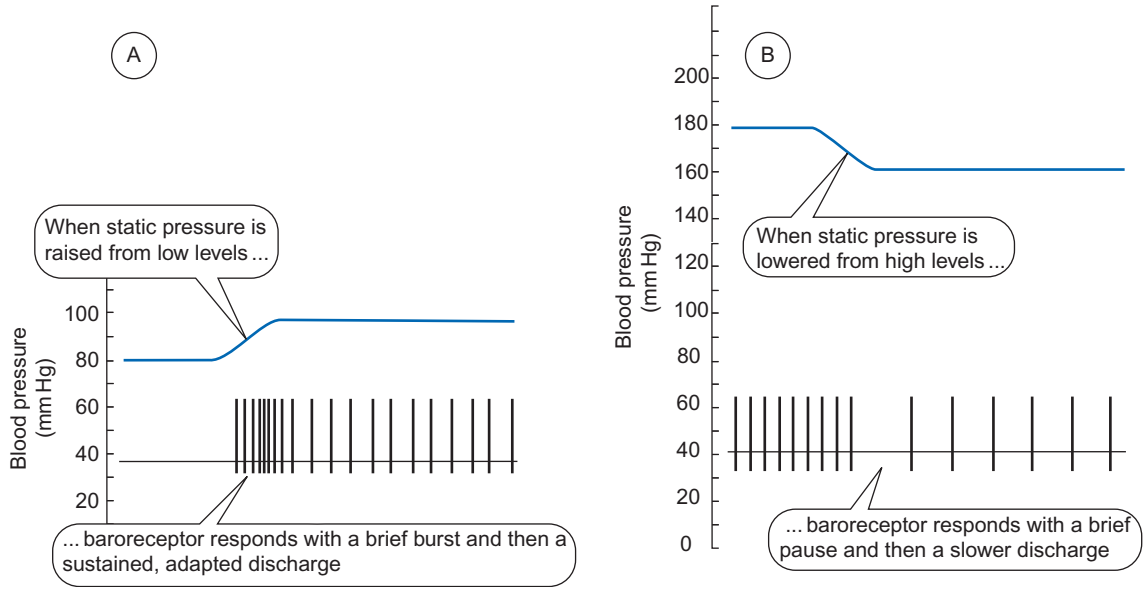

FIGURE 5.13.3 Response of the baroreceptors to changes in static pressure. When pressure is raised from low levels, there is a brief, rapid burst of impulses followed by a sustained but slower discharge rate. Thus, the receptors show a partial adaptation. Conversely, when pressure is lowered from a high level, there is a brief pause followed by sustained, slower rate of discharge. The responses are shown from single myelinated baroreceptor afferents from cat carotid sinus. (Source: *Adapted from S. Landgren,* Acta Physiologica Scandinavica ***26****:1—34, 1952.*)

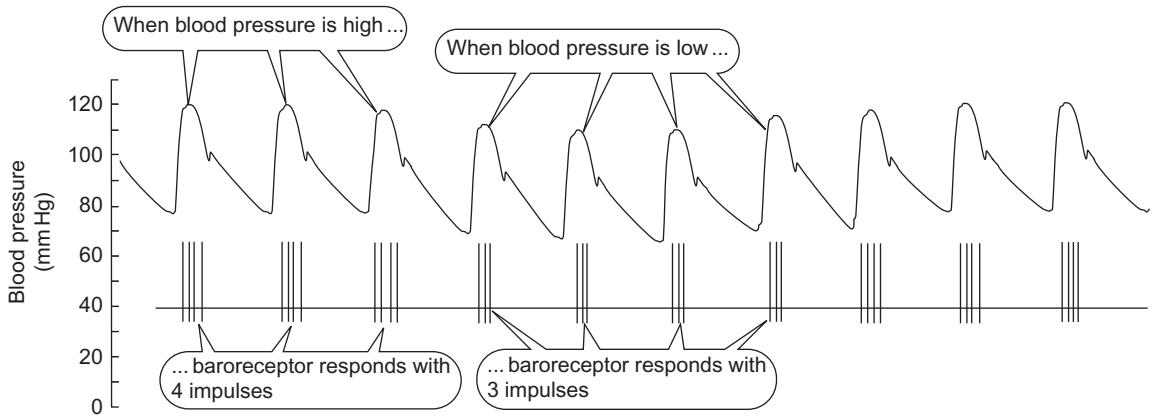

FIGURE 5.13.4 Response of a baroreceptor afferent to the pulse. Recordings are from a single afferent baroreceptor from a rabbit aorta. When the arterial pressure is high, the baroreceptor responds with 4 impulses. When the pressure is slightly lower, it responds with 3. Summation of responses from many fibers allows for a graded response of the average pressure and of the pulse pressure. (Source: *Modified from S.E. Downing,* Journal of Physiology ***150****:210—213, 1960.*)

CO and TPR, the consequence of the baroreflex is to reduce arterial pressure toward normal.

Reduced arterial blood pressure engages the opposite response of the baroreflex to increased blood pressure. The firing frequency of the baroreceptors decreases and engages the brain stem to cause:

1. Increased heart rates due to decreased parasympathetic stimulation of the SA node along with increased sympathetic activity. The **tachycardia** is accompanied by **increased myocardial contractility**.
2. Increased sympathetic output causes vasoconstriction and a **rise in TPR**. Both of these raise the blood pressure toward normal.

The baroreflex is a negative feedback mechanism that corrects acute changes in blood pressure. It acts rapidly. The delay between an increase in high blood pressure and bradycardia is about 0.5 s, and the delay between high blood pressure and vasodilation is about 1.5 s.

THE BAROREFLEX MEDIATES PARASYMPATHETIC AND SYMPATHETIC OUTPUT FROM CENTERS LOCATED IN THE MEDULLA

SENSORY AFFERENTS TERMINATE IN THE NUCLEUS TRACTUS SOLITARIUS

The dorsal—medial medulla contains an elongated nucleus of cells called the **nucleus tractus solitarius (NTS)**, which is the terminus of nearly all of the

cardiovascular afferents including the baroreceptors, cardiopulmonary afferents, arterial chemoreceptors, and pulmonary stretch receptors. Sensory integration of these various signals occurs here, and the NTS sends its output to the **nucleus ambiguus (NA)**, the **caudal ventrolateral medulla (CVLM)**, and the **hypothalamus**.

NTS TONICALLY INHIBITS HEART RATE THROUGH VAGAL EFFERENTS

Vagal efferents originating mainly in the **nucleus ambiguus**, but some in the **dorsal motor nucleus** of the vagus in the medulla, inhibit the heart rate by reducing the slope of the pacemaker potential in SA nodal cells. Baroreceptors tonically activate cells in the NTS, and this tonic excitation is relayed to the nucleus ambiguus where vagal efferents are tonically active. Thus **in humans there is a constant vagal tone** that continuously inhibits the heart rate. Reductions in blood pressure relieve this tonic inhibition, thereby accelerating the heart rate by removing parasympathetic tone. This completes a negative feedback loop: the accelerated heart rate increases the cardiac output and tends to restore the blood pressure. When blood pressure rises, the reverse occurs: NTS stimulates the NA more and there is greater vagal inhibition of heart rate (see Figure 5.13.5).

SYMPATHETIC STIMULATION OF THE HEART IS THROUGH THE ROSTRAL VENTROLATERAL MEDULLA

The output of the NTS also goes to the CVLM, where it stimulates inhibitory connections to the rostral ventrolateral medulla, RVLM. The RVLM connects to sympathetic preganglionic neurons in the interomedial gray of the thoracic spinal cord. Thus, decreased blood pressure that is sensed by the baroreceptors reduces the output of the NTS to the CVLM, which relieves its inhibition of the RVLM, thereby increasing sympathetic stimulation of the heart and the vessels. This accelerates the heart rate and vasoconstricts, both of which tend to restore the decrease in blood pressure. When blood pressure rises, the opposite occurs: increased activation of the inhibition of CVLM on RVLM causes reduces sympathetic outflow to the heart and vessels.

PARASYMPATHETIC WITHDRAWAL ACCELERATES THE HEART FASTER THAN SYMPATHETIC STIMULATION

In humans, there is continual parasympathetic tone. Its effect is much faster than the sympathetic effects, so that acceleration of heart rate in the short-term regulation of blood pressure is typically first accomplished by either removal of parasympathetic tone (when blood pressure falls) or adding to the parasympathetic tone when blood pressure rises.

INSPIRATION INFLUENCES HEART RATE—THE *RESPIRATORY SINUS ARRHYTHMIA*

If one continuously monitors heart rate and blood pressure in a resting person, one quickly observes a regular oscillation in both heart rate and blood pressure due to breathing. This is called the **respiratory sinus arrhythmia**. Fourier analysis of the frequency of the R–R interval, as an immediate indicator of heart rate, shows that the main power in the frequency spectrum is at the heart rate, around 70 bpm, and the second source of power is in the respiratory rhythm, around 12 bpm. The **heart**

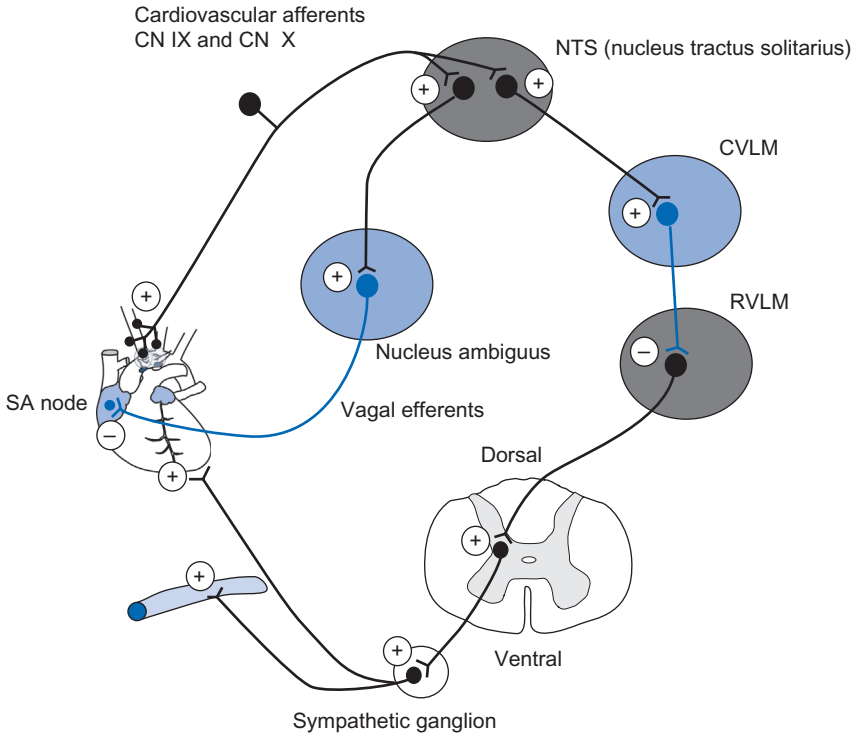

FIGURE 5.13.5 Central pathways for control of heart rate and blood pressure. Cardiac and baroreceptor afferents terminate on cells in the NTS in the medulla, entering over the glossopharyngeal nerve (CN IX) and the vagus (X). These cells send excitatory connections to the nucleus ambiguus which, along with the dorsal motor nucleus of the vagus, sends inhibitory connections over the right vagus to the SA node. Cells in the NTS also excite cells in the CVLM, which inhibit cells in the RVLM, which reduces excitation of sympathetic preganglionic cells in the thoracic spinal cord.

rate accelerates during inspiration and slows during expiration. This is due to connections to the vagal nuclei from the inspiratory centers in the medulla. These connections hyperpolarize the cardiac motor neurons in the NTS, inhibiting their response to the baroreceptors. This causes the acceleration of the heart rate during inspiration. This effect is shown diagrammatically in Figure 5.13.6.

HIGHER CENTERS INFLUENCE BLOOD PRESSURE AND HEART RATE

Everyday experience shows that emotional stress and fear markedly affect both heart rate and blood pressure. The alerting response is a stereotypical response to a dangerous or threatening environmental stimulus. It typically involves

- tachycardia, with attendant increased cardiac output;
- vasodilation of skeletal muscle;
- vasoconstriction of visceral perfusion (skin, splanchnic, and renal circulation);
- increased blood pressure and reduced sensitivity to the baroreceptor reflex.

The brain regions involved in this effect are distributed along the central long axis of the brain, being found in the amygdala, hypothalamus, and periaqueductal gray matter.

LONG-TERM REGULATION OF BLOOD VOLUME DETERMINES LONG-TERM REGULATION OF BLOOD PRESSURE

The main idea for long-term regulation of blood pressure is this: if you put more blood into the system, the pressure goes up; if you remove blood from the system, the pressure goes down. This is true only if the caliber of the blood vessels does not change. In the short term, the caliber of the vessels does change, which is the basis for sympathetic regulation of the blood pressure. In the short term, the heart rate (and therefore cardiac output) can change, and this is the basis of parasympathetic regulation of blood pressure. If we change the blood volume, we can change the baseline on which these regulations occur. The long-term regulation of the blood volume involves hormonal regulation of renal function.

A block diagram illustrating the components of long-term regulation is shown in Figure 5.13.7. The diagram is explained sequentially in terms of its blocks here.

Block I: The Blood Volume–Mean Systemic Pressure Relation

The mean systemic pressure is the pressure when the heart is stopped and all flow stops. It is the pressure that the system would have if it were filled to the indicated blood volume and under the indicated conditions. This curve can be shifted by changes in the caliber of the arteries or veins, such as occurs during sympathetic venoconstriction.

Block II: The Mean Systemic Pressure–Cardiac Output Relation

The mean systemic pressure forms the *x*-intercept of the vascular function curve. Along with the TPR and relative compliances, this determines the vascular function curve. Its point of intersection with the cardiac function curve determines the operating point of the entire system, which is the cardiac output (CO), equal to the venous return.

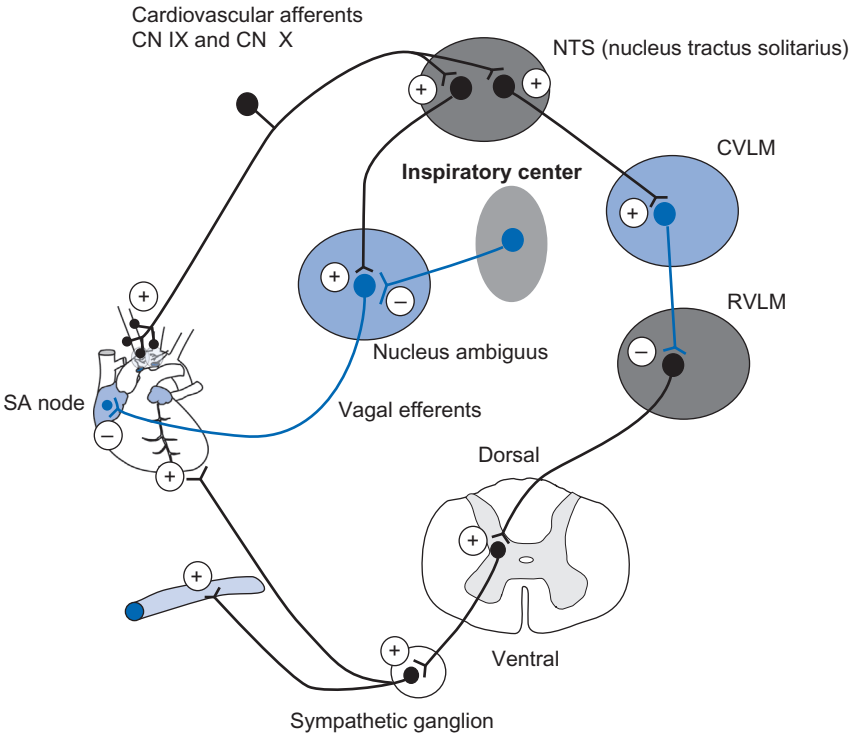

FIGURE 5.13.6 Origin of the respiratory sinus arrhythmia. During inspiration, the heart rate accelerates. This is thought to be due to inhibitory connections from the inspiratory center to cardiac motor neurons in the nucleus ambiguus. These connections momentarily desensitize the cells to the baroreceptor input, so that there is less brake on the heart, and therefore an acceleration of the heart during inspiration.

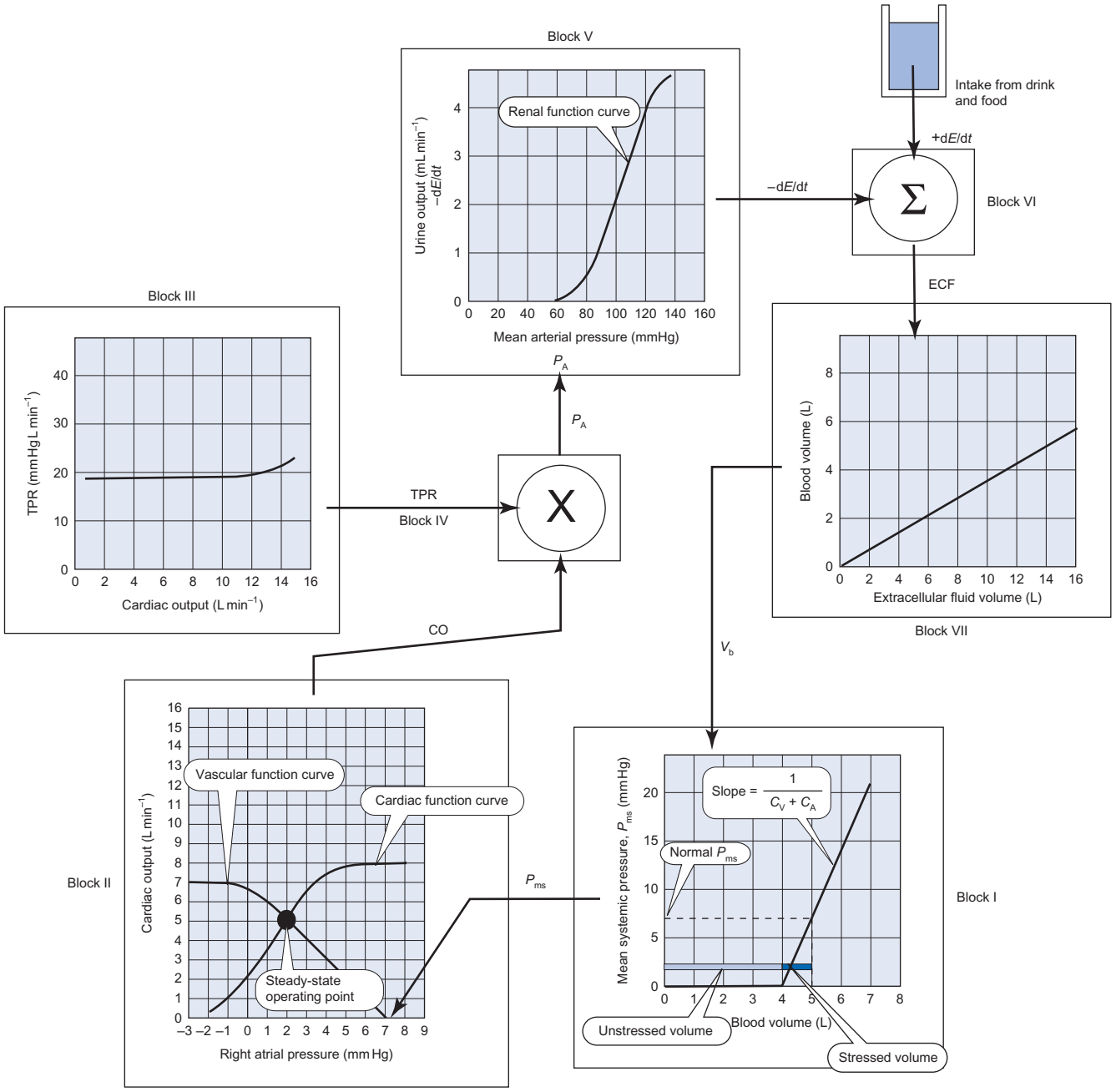

FIGURE 5.13.7 Block diagram of long-term control of arterial pressure. For details, see text.

Block III: The Cardiac Output–TPR Relationship

The TPR converts cardiac output, CO, into the mean arterial pressure. The main determinant of TPR is the caliber of the resistance vessels, the arterioles. What affects the caliber of these vessels was discussed in Chapter 5.12. TPR is independent of CO until CO gets large.

Block IV: $P_A = CO \times TPR$

The mean arterial pressure, P_A, can be calculated as $P_A = CO \times TPR$. This is an empirical relationship, not a causal one, because the variables are not independent.

Block V: The Renal Function Curve

The renal function curve relates urinary output to mean arterial pressure. The curve shown is the approximate normal curve. This is not a causal relationship but reflects the fact that both P_A and urinary excretion increase with circulatory volume. Increasing volume increases both P_A and the rate of urinary excretion, but there is a threshold between 60 and 80 mmHg below which urinary output ceases. Fluid lost from the kidney directly derives from the extracellular fluid (ECF), but this fluid also exchanges with the intracellular fluid. Thus, urinary excretion represents an equivalent volume of the ECF, with Na as its most important component,

because Na content determines the ECF. The renal function curve is influenced by several hormones including **antidiuretic hormone** (ADH), the **renin–angiotensin–aldosterone** (RAA) system, and **atrial natriuretic peptide** (ANP).

Block VI: ECF Volume Is the Integral of Excretion and Intake

While some ECF volume is being lost by excretion in the urine, additional fluid is taken into the body in food and drink. The ECF is the sum of fluid gains and losses.

Block VII: The Blood Volume–Extracellular Fluid Volume Relationship

The ECF volume is the sum of the plasma volume and interstitial fluid volume. Plasma makes up about 58% of the blood volume. Blood volume is typically about 5 L, whereas ECF volume is about 14 L. Thus blood comprises about 36% of the ECF volume. Expansion of the ECF generally means expansion of the blood volume, and contraction of the ECF volume generally means contraction of the blood volume.

All of these blocks interact to produce the observed cardiac output, arterial pressure, and renal output. The systems will interact to find the steady state in which the net change to the blood volume will be zero. We will consider several perturbations of this system to illustrate its operation.

SYMPATHETIC TETRALOGY

General sympathetic stimulation exerts several cardiovascular effects. These include:

- increased heart rate;
- increased cardiac contractility;
- vasoconstriction;
- venoconstriction.

These effects are indicated in the systems diagram as shown in Figure 5.13.8.

- **Venoconstriction increases P_{ms}.** As shown in Block I, venoconstriction increases the stressed volume—it shifts the curve relating P_{ms} to blood volume to the left.
- **Vasoconstriction changes the slope of the vascular function curve.** Venoconstriction increases P_{ms}, and this shifts the vascular function curve upward. At the same time, vasoconstriction increases TPR, which decreases the slope of the vascular function curve (Block II).
- **Sympathetic stimulation rotates the cardiac function curve counterclockwise.** Sympathetic stimulation increases the force of cardiac contraction and also increases the heart rate. Both of these effects markedly increase the cardiac output for a given input. This raises the cardiac function curve and rotates it counterclockwise. (Block II).
- **Sympathetic stimulation shifts fluid from interstitial fluid to blood.** Constriction of the arterioles reduces the pressure downstream in the capillaries. This reduces the net driving force for filtration of fluid out of the capillaries and increases the movement of fluid from the interstitial fluid into the blood. This is a relatively small effect (Block VII). In addition, sympathetic constriction of renal arterioles reduces urinary excretion, preventing loss of circulatory volume and maintaining blood pressure.

HORMONAL REGULATION OF BLOOD PRESSURE

Figure 5.13.7 should clarify a central truth relating to the arterial blood pressure: it depends on the state of contraction of the arteries and how much blood is in them. How much blood is in them is the blood volume. If you reduce the blood volume, you reduce the mean systemic pressure, which lowers the vascular function curve, which lowers CO and lowers P_A. Similarly, raising the blood volume raises P_{ms} and raises the vascular function curve, which raises CO and raises P_A. The blood volume is controlled by several hormones working in concert. These are:

- RAA system hormones
- ADH
- ANP.

RAA SYSTEM

As discussed in Chapter 5.11, the RAA system begins with the secretion of the enzyme **renin** by granule cells in the afferent arteriole of the glomeruli of the kidney. Renin is secreted in response to three stimuli:

1. Renal sympathetic nerves stimulate renin release.
2. Decreased distal tubule [Na^+] stimulates renin release.
3. Decreased afferent arteriolar pressure stimulates renin release.

Renin cleaves an α_2 macroglobulin in blood called **angiotensinogen**, which is made by the liver, to form **angiotensin I**, a 10 amino acid peptide. **Angiotensin converting enzyme**, **ACE**, cleaves off 2 more amino acids to make **angiotensin II**. Angiotensin II has four major effects:

1. vasoconstriction;
2. release of aldosterone from the adrenal cortex;
3. increasing the sensation of thirst;
4. Release of ADH.

All of these effects counteract the cause of the initial stimulus for renin release, which was reduced afferent arteriolar pressure or reduced perfusion of the kidney. The angiotensin II causes vasoconstriction, which tends to raise blood pressure back toward normal. More importantly, the aldosterone that is released from the adrenal cortex increases Na^+ reabsorption from the kidney, and thereby reduces renal excretion of Na^+. Since Na^+ is the major extracellular ion, retention of Na^+

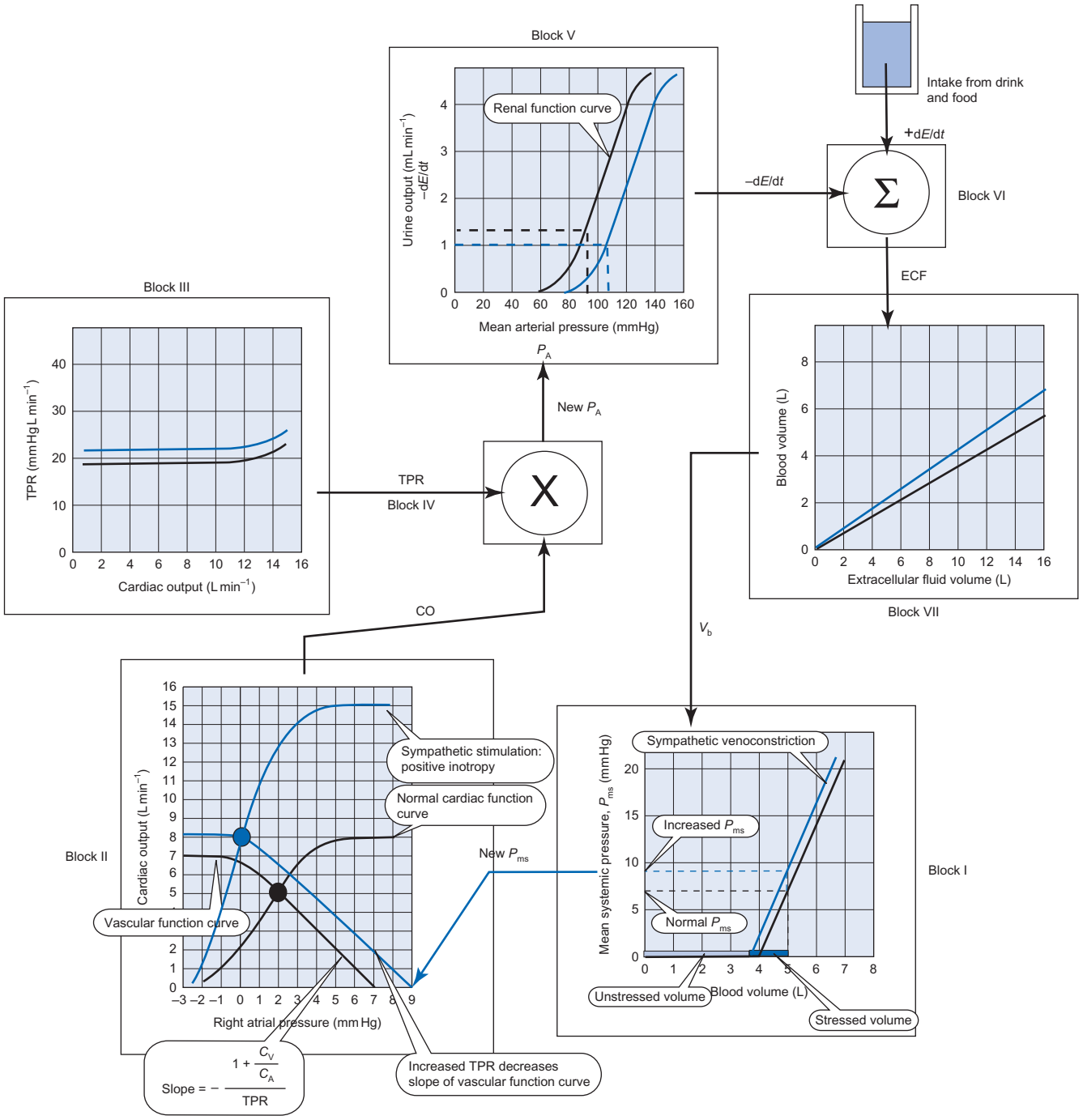

FIGURE 5.13.8 Effects of sympathetic stimulation on the cardiovascular–renal system. Venoconstriction increases P_{ms} according to Block I. The increased P_{ms} causes an upward shift in the vascular function curve, whose slope is simultaneously decreased by the increase in TPR caused by sympathetic vasoconstriction. Sympathetic stimulation increases the contractility of the heart and also its rate, rotating the cardiac function curve up and to the left (Block II). These effects on cardiac and vascular function curves cause an increase in cardiac output. The increased output along with the increased TPR (Block III) causes an increase in the arterial pressure. The increased arterial pressure increases urinary excretion according to the normal renal function curve (Block V), but sympathetic stimulation shifts the curve to the right, reducing urinary loss for a given pressure. Constriction of the arterioles causes a reduction in the capillary pressure that favors filtration out of the capillaries and into the interstitial space. This favors more blood volume per unit of ECF volume (Block VII).

retains ECF. This raises the blood volume and restores blood pressure and perfusion. **The overall effect of the RAA system is to shift the renal function curve to the right.** This effect is illustrated in Figure 5.13.9.

ANTIDIURETIC HORMONE

ADH is also known as **vasopressin**. ADH constricts blood vessels and reduces urine output. ADH is a 9 amino acid peptide synthesized in cells in the supraoptic nucleus and paraventricular nucleus in the hypothalamus. It travels

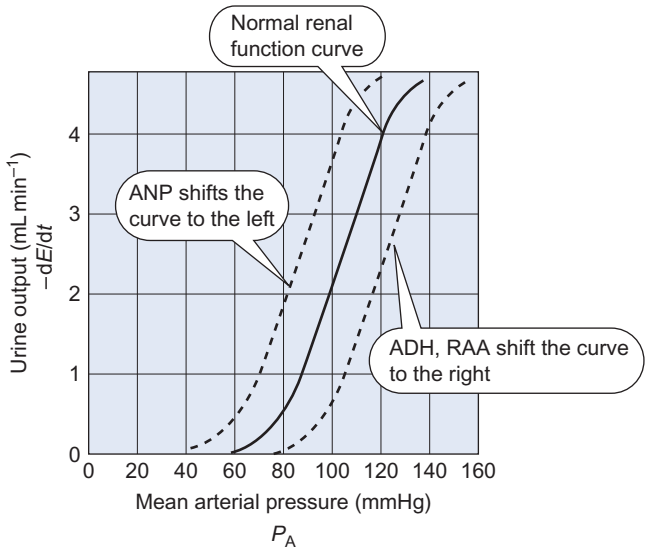

FIGURE 5.13.9 Effects of hormones on the renal function curve. ADH increases the reabsorption of water by the kidneys so that the kidney excretes a small volume of highly concentrated urine. This has the effect of reducing the extracellular volume excreted at any given pressure: this equates to a shift in the renal function curve to the right. The RAA system reduces the excretion of Na^+, which means it reduces the volume of ECF excreted by the kidney. ANP promotes the excretion of water and salt, so it shifts the renal function curve to the left.

down the axons of these cells and is secreted in the posterior pituitary in response to **hypovolemia** and to **plasma hyperosmolarity**. Thus, it helps prevent further hypovolemia by preventing, as much as possible, further loss of fluid through the urine. It retains water but not salt, so that aldosterone and ADH both tend to increase the ECF volume by limiting urinary excretion, but they do so through entirely different mechanisms that allow differential excretion of water or salt. **The overall effect of ADH is also a shift of the renal function curve to the right.** This effect is illustrated in Figure 5.13.9.

ATRIAL NATRIURETIC PEPTIDE

ANP is a 28 amino acid peptide that is secreted by atrial cells in response to stretch. The atria stretch more when right atrial pressure is high, which occurs when blood volume expands and P_{ms} increases. This shifts the vascular function curve upward and raises P_{RA}. ANP stimulates salt and water excretion to rid the body of the excess fluid. Thus, **ANP shifts the renal function curve to the left**.

Clinical Applications: Hypertension

Hypertension is defined as an abnormally elevated blood pressure. Since blood pressure is elevated during activity, its definition centers on resting blood pressure. The diagnosis of hypertension requires three successive measurement of high blood pressure on three separate visits to the physician's office, separated each by at least a week. Often hypertension is asymptomatic, but its control is vitally important for a number of chronic diseases including heart disease, myocardial infarction and heart failure, stroke, and kidney failure. The classification of hypertension is shown in Table 5.13.1.

Essential hypertension has no readily identifiable cause, whereas secondary hypertension, by definition, results from an identifiable cause such as Cushing's syndrome (overproduction of glucocorticoids, see Chapter 9.5), hyperthyroidism, pheochromocytoma (overproduction of epinephrine by the adrenal gland), and preeclampsia. Although there is no identifiable cause in essential hypertension, known risk factors include sedentary lifestyle, smoking, stress, obesity, salt intake, alcohol intake, and genetics.

The general treatment of hypertension is two fold: modification of lifestyle and pharmacological. Lifestyle modification include loss of weight, reduction of salt intake, exercise, stress reduction, limitation of alcohol intake and smoking.

Pharmacological intervention aims to reduce the stressed volume by reducing overall ECF volume, thereby reducing mean systemic pressure and lowering the vascular function curve. This will lower cardiac output at the same TPR. Other drugs aim to reduce TPR. Drugs used to treat hypertension include:

1. **ACE inhibitors.** These prevent the formation of angiotensin II from angiotensin I and thereby remove a potent vasoconstrictor and also reduce aldosterone secretion. This tends to waste Na^+ and reduce the ECF volume. Other drugs block the angiotensin II receptor (ARB, such as losartan) that prevents the vasoconstrictor effects of angiotensin II.
2. **Diuretics.** Hydrochlorothiazide inhibits salt reabsorption in the distal nephron (see Chapter 7.5); loop diuretics such as furosemide also waste Na^+ and excrete more of the ECF.
3. **Beta blockers** such as labetolol antagonize the effects of circulating epinephrine on beta receptors, reduce heart rate and cardiac contractility to reduce cardiac output, and thereby reduce mean arterial pressure.
4. **Calcium channel blockers** such as amlodipine block voltage-gated Ca^{2+} entry into smooth muscle cells, thereby causing vasodilation and reduction in TPR, so causing reduced mean arterial pressure.

TABLE 5.13.1 Classification of Hypertension

	Normal	Prehypertensive	Stage 1	Stage 2
Systolic (mmHg)	90–119	120–139	150–159	>160
Diastolic (mmHg)	60–79	80–89	90–99	>100

SUMMARY

The average arterial pressure originates from the heart pumping blood from the venous side of the circulation to the arterial side. The pulse pressure derives from the ejection of a volume of blood, along with the compliance of the arteries and the TPR.

Regulation of the average arterial blood pressure is accomplished in the short run through the baroreceptor reflex. In the long run it is accomplished by regulation of the volume of ECF by the kidneys.

The baroreceptors are stretch receptors located in the carotid body at the bifurcation of the internal and external carotid arteries, and in the aortic arch. Different receptors respond at different pressure levels, so that response is assured over a wide range of pressure. These receptors typically respond to the systolic pressure and are silent during the lower, diastolic pressure wave.

Sensory afferents from the carotid body and aortic bodies travel over the glossopharyngeal nerve, CN IX, and the vagus nerve, CN X, respectively, to make connections within the NTS in the medulla. Their firing rate is approximately proportional to the pressure. Cells in the NTS send fibers to the nucleus ambiguus, which in turn forms the efferent limb of the vagus nerve. These send parasympathetic fibers to the SA node through the right vagus nerve. Thus increased blood pressure activates cells in the NTS which in turn activate cells in the nucleus ambiguus, which reflexly slows the heart rate through parasympathetic efferents. When blood pressure falls, tonic parasympathetic stimulation is removed, relieving the heart of its brake, and therefore accelerating the heart rate. This increases cardiac output, which raises arterial pressure back toward normal.

The baroreceptor reflex also influences sympathetic outflow. The NTS makes contact with cells in the CVLM which sends inhibitory connections to the RVLM which activates sympathetic preganglionic interneurons in the spinal cord. Thus, increases in arterial pressure cause an increase in the firing rate of the baroreceptors which increases inhibition of the RVLM by CVLM, which inhibits sympathetic outflow to the heart and vasculature. This contributes to bradycardia and vasoconstriction, both of which tend to restore the blood pressure toward normal.

The inspiratory center is active during inspiration, and it sends collateral fibers to inhibit cells in the nucleus ambiguus that drive parasympathetic efferents to the heart. Inspiration therefore inhibits parasympathetic tone, which accelerates the heart rate during inspiration. This effect is called the **respiratory sinus arrhythmia**.

Long-term regulation of blood pressure is achieved by regulating the volume of the ECF and its distribution between veins and arteries. Regulation of the ECF volume is controlled by hormones including ADH, the RAA system, and ANP.

REVIEW QUESTIONS

1. Where are the baroreceptors located? How do they respond to arterial pressure? Why are there two types of baroreceptors?
2. What is the baroreflex? What is the cardiovascular response to high blood pressure? Low blood pressure? What mediates bradycardia? What mediates tachycardia?
3. What is respiratory sinus arrhythmia? Is the heart rate faster during inspiration or expiration? Why?
4. What regulates blood pressure in the long term?
5. Diuretics increase urinary excretion at any arterial pressure. Why do these aid in controlling blood pressure?
6. What is the sympathetic tetralogy? Does this regulate blood pressure or is it used to keep pressure high? Why would you want high blood pressure?
7. What is renin? What causes its release? What does it do?
8. What is aldosterone? What causes its release? What does it do?
9. What is ADH? What causes its release? What does it do?