CASE 13

A 57-year-old man with long-standing diabetes mellitus and newly diagnosed hypertension presents to his primary care physician for follow-up. The patient has been trying to alter his dietary habits and now exercises more frequently, but the hypertension has persisted. The patient is started on an angiotensin-converting enzyme inhibitor (ACE inhibitor) with good results. He is instructed to continue this medication and follow up in several months.

◆ What neural and humoral pathways regulate arterial pressure?

◆ What are two effects of angiotensin II?

◆ How would inhibition of ACE decrease blood pressure?
ANSWERS TO CASE 13: REGULATION OF ARTERIAL PRESSURE

Summary: A 57-year-old diabetic man is diagnosed with hypertension that is not controlled with lifestyle changes and requires medication (an ACE inhibitor).

◆ There are two pathways for the regulation of arterial blood pressure:
  ◆ **Neural:** Baroreceptor reflex (fast acting).
  ◆ **Humoral:** Renin-angiotensin-aldosterone system (slow acting).

  ◆ **Effects of angiotensin II:** Stimulates the adrenal cortex to synthesize and secrete aldosterone and causes vasoconstriction of the arterioles.
  ◆ **Inhibition of ACE:** Prevents conversion of angiotensin I to angiotensin II.

CLINICAL CORRELATION

The 57-year-old patient in this case has diabetes and hypertension. Tight control of the blood sugars helps slow down both the microvascular (small vessel) disease and macrovascular (atherosclerotic) disease. Aggressive control of the hypertension is also vital, particularly in helping to prevent heart disease and renal complications. In diabetic patients, ACE inhibitors are usually the best agents. ACE inhibitors stop the conversion of angiotensin I to angiotensin II. Decreased angiotensin II causes decreased secretion of aldosterone and decreased vasoconstriction of the arterioles, resulting in decreased blood pressure. Studies have shown that for diabetic patients with microalbuminuria, ACE inhibitors can slow progression to renal failure. Possible side effects for all ACE inhibitors include a cough, hyperkalemia, reversible decreased renal function, and, rarely, angioedema.

APPROACH TO ARTERIAL PRESSURE PHYSIOLOGY

Objectives

1. Discuss the determinants of mean arterial pressure (MAP).
2. Describe the baroreceptor reflex.
3. Describe the renin-angiotensin-aldosterone system.
4. Describe the effects of aldosterone on renal function and arterial blood pressure.

Definitions

**MAP:** The blood pressure in the large arteries averaged over time.

**Total peripheral resistance (TPR):** The resistance to blood flow in the systemic circulation.

**Baroreceptor reflex:** A neural reflex involved in the short-term regulation of arterial blood pressure.
DISCUSSION

MAP is determined by the interplay of TPR and cardiac output (CO), as is given by the equation

\[ \text{MAP} = \text{TPR} \times \text{CO} \]

In reality, the equation should read \((\text{MAP} - \text{VP}) = \text{TPR} \times \text{CO}\) where VP is venous pressure. However, VP is so low (0-5 mm Hg) that it generally is ignored in the equation. Although VP can be ignored in this situation, it is of vital importance and cannot be ignored when the regulation of CO is considered (see Case 12).

TPR is due mostly to the resistance to flow offered by the small arteries and arterioles in the various vascular beds. These vessels are composed in large part by smooth muscle that contracts in response to the sympathetic nerve neurotransmitter norepinephrine and to the circulating hormones epinephrine, angiotensin II, and antidiuretic hormone (ADH, or vasopressin), among others. Contraction decreases vessel radius, thus increasing resistance to flow.

In young and middle-aged individuals, arterial blood pressure normally is maintained around 120/80 mm Hg. Hypertension currently is defined as systolic pressures of 140 mm Hg or more and/or diastolic pressures of 90 mm Hg or more. Regulation of blood pressure within rather narrow limits or set points is accomplished through a complex system of neural and humoral mechanisms that are not completely understood. Even less is known about the genetic and environmental factors that determine the set points.

Arterial pressure is determined by the interplay of CO and TPR. Thus, factors that influence either or both will influence blood pressure. One of the major factors is the autonomic nervous system. Afferent nerves that behave as stretch receptors (baroreceptors) are located mainly in the carotid sinus and the aortic arch and respond to intraluminal pressure. Nerve impulses from these receptors arrive and are processed in the brainstem. Regions within the brainstem then regulate the activities of sympathetic and parasympathetic efferent nerves, which in turn regulate both CO and TPR.

The sinoatrial (SA) and atrioventricular (AV) nodes of the heart are innervated by both sympathetic and parasympathetic efferent nerves. Norepinephrine released locally from sympathetic nerves and norepinephrine and epinephrine arriving from the adrenal gland increase the rate of depolarization of the SA node and increase conduction through the AV node, thus increasing heart rate. The same substances also stimulate receptors on myocardial cells to increase contractility. In contrast, acetylcholine (ACh) released locally from parasympathetic nerves decreases the rate of depolarization of the SA node and conduction through the AV node, thus decreasing heart rate. There appears to be minimal parasympathetic innervation of contractile myocardial cells; however, the decrease in heart rate itself will result in a
decrease in myocardial contractility. As discussed in Case 12, changes in both heart rate and contractility can lead to changes in CO and thus MAP.

Arteries, especially arterioles, and veins are innervated by sympathetic nerves. Norepinephrine released from these nerves and norepinephrine and epinephrine released from the adrenal gland contract arteries to regulate TPR. As discussed in Case 12, changes in TPR directly affect MAP. Norepinephrine and epinephrine also contract veins to regulate mean circulatory filling pressure. As discussed in Case 12, changes in mean circulatory filling pressure affect venous pressure, which in turn affects CO and thus MAP.

The neural reflex described above, which is called the baroreceptor reflex, can respond rapidly to changes in MAP brought on by normal activity and by pathologic conditions such as those characterized by blood loss. For example, as a result of the forces of gravity, merely going from a supine to an upright position will cause a rapid increase in pressure in vessels of the lower extremities and a decrease in pressure in vessels of the upper extremities, including the carotid arteries. The increase in pressure in the veins below the heart leads to an increase in unstressed volume, a decrease in central venous pressure, and a decrease in CO (see Case 12). This decrease in CO decreases MAP to decrease the pressure in the carotid arteries further. The decreased pressure in the carotid sinus is sensed rapidly by the baroreceptors to initiate the reflex release of norepinephrine and epinephrine. These chemical mediators in turn rapidly contract the veins, thus increasing venous pressure, and rapidly increase heart rate and contractility; together, these changes increase CO. The mediators also contract the arterioles, rapidly increasing TPR. The increased CO and increased TPR quickly return MAP to the normal value, thus maintaining cerebral blood flow.

A second major factor regulating blood pressure is the hormonal renin-angiotensin-aldosterone system. Renin is an enzyme that is synthesized and stored in cells lining the renal afferent arteriole at the point where it contacts the thick ascending limb of the loop of Henle of the nephron in a region called the juxtaglomerular apparatus. Renin is secreted into the bloodstream in response to norepinephrine released from sympathetic nerves distributed to the afferent arteriole, to a decrease in afferent arteriolar pressure (the cells act as baroreceptors), and to unknown paracrine signals from cells that line the thick ascending limb of the loop of Henle. These paracrine signals are released in response to the rate of flow and the composition of the tubular fluid. Once released, renin cleaves the circulating \( \alpha_2 \) globulin angiotensinogen to yield angiotensin I. Angiotensin I is relatively inactive itself, but it is cleaved rapidly by ACE to yield angiotensin II. ACE is found in many tissues but is present in relatively high amounts in the lung. Circulating angiotensin II has two major actions: It is a potent stimulator of arteriolar smooth muscle contraction, and thus it increases TPR. This is a relatively rapid response, but not as rapid as the baroreceptor reflex. Perhaps more important for the long-term regulation of blood pressure, angiotensin II stimulates the release of aldosterone from the adrenal cortex. As discussed in Case 22, aldosterone...
increases the reabsorption of sodium and water from the nephron. Thus, more of the salt and water that are ingested are retained, resulting in the expansion of blood and interstitial volume. The increase in extracellular volume, along with other actions that are understood less fully, results in a long-term increase in MAP.

**COMPREHENSION QUESTIONS**

[13.1] Patients with elevated MAP often are prescribed drugs that inhibit angiotensin-converting enzyme (ACE). Which of the following findings is most likely to be observed in patients on these drugs alone?

A. A further increase in TPR
B. Increased plasma renin levels
C. Decreased sympathetic nerve activity
D. Decreased plasma angiotensin I levels
E. Increased plasma aldosterone levels

[13.2] Licorice contains a chemical that enhances the aldosterone-like effects of cortisol. Thus, patients who ingest large amounts of licorice (which is an ingredient in some herbal medicines as well as a candy) will likely exhibit which of the following?

A. Increased blood pressure
B. Increased plasma renin levels
C. Increased plasma aldosterone levels
D. Increased TPR
E. Decreased central venous pressure

[13.3] In response to the loss of blood, compensatory mechanisms come into play at various times to blunt decreases in MAP and restore blood volume to normal. Which of the following most accurately depicts the temporal order of effectiveness of three of these mechanisms, from earliest to latest?

A. Aldosterone, sympathetic nerves, angiotensin II
B. Angiotensin II, aldosterone, sympathetic nerves
C. Angiotensin II, sympathetic nerves, aldosterone
D. Sympathetic nerves, aldosterone, angiotensin II
E. Sympathetic nerves, angiotensin II, aldosterone

**Answers**

[13.1] B. Inhibition of ACE will reduce the formation of angiotensin II, a constrictor of arteriolar smooth muscle, thus reducing TPR. The decreased angiotensin II also will lead to a decrease in aldosterone secretion. However, the decrease in angiotensin II and in mean arterial blood pressure will result in an increase in plasma renin and angiotensin I concentrations and an increase in sympathetic nerve activity.
A. The aldosterone-like effects induced by licorice will result in NaCl and water retention and an expansion of blood volume. This will lead to an increase in venous pressure, CO, and MAP. Plasma levels of both renin and aldosterone will be decreased.

E. As part of the baroreceptor response, sympathetic nerve activity will increase almost immediately in response to the decrease in MAP induced by the loss of blood. The increased sympathetic nerve activity and the reduced renal arterial pressure will result quickly in the secretion of renin, which initiates a cascade that results in the production of angiotensin II, a powerful constrictor of arterial smooth muscle. Although angiotensin II will induce the secretion of aldosterone rather quickly, the onset of action of aldosterone is rather slow because expression of its actions requires the synthesis of proteins in renal epithelial cells.

**PHYSIOLOGY PEARLS**

❖ The level of MAP is determined by the interplay between TPR and CO, as given by the equation

\[
\text{MAP} = \text{TPR} \times \text{CO}
\]

❖ TPR is determined primarily by the state of contraction of the small arteries and arterioles.

❖ Rapid reflex changes in CO and TPR are accomplished through activation of the sympathetic nervous system.

❖ Longer term regulation of CO and blood pressure results from regulation of extracellular (blood) volume by the renin-angiotensin-aldosterone pathway.

**REFERENCES**
