CHAPTER 14

# Adrenergic Agonists & Antagonists

## KEY CONCEPTS

1. Adrenergic agonists can be categorized as direct or indirect. Direct agonists bind to the receptor, whereas indirect agonists increase endogenous neurotransmitter activity.
2. The primary effect of phenylephrine is peripheral vasoconstriction with a concomitant rise in systemic vascular resistance and arterial blood pressure.
3. Clonidine seems to decrease anesthetic and analgesic requirements and to provide sedation and anxiolysis.
4. Dexmedetomidine is a lipophylic α-methylol derivative with a higher affinity for $\alpha_2$-receptors than clonidine. It has sedative, analgesic, and sympatholytic effects that blunt many of the cardiovascular responses seen during the perioperative period.
5. Long-term use of these agents, particularly clonidine and dexmedetomidine, leads to supersensitization and up-regulation of receptors; with abrupt discontinuation of either drug, an acute withdrawal syndrome manifested by a hypertensive crisis can occur.
6. Ephedrine is commonly used as a vasopressor during anesthesia. As such, its administration should be viewed as a temporizing measure while the cause of hypotension is determined and remedied.
7. Small doses (approximately 2 mcg/kg/min) of dopamine (DA) have minimal adrenergic effects but activate dopaminergic receptors. Stimulation of these nonadrenergic receptors (specifically, $DA_1$ receptors) vasodilates the renal vasculature and promotes diuresis.
8. Favorable effects on myocardial oxygen balance are believed to make dobutamine a good choice for patients with the combination of congestive heart failure and coronary artery disease, particularly if peripheral vascular resistance is elevated. (There are some recent debates regarding this beneficial effect.)
9. Labetalol lowers blood pressure without reflex tachycardia because of its combination of α- and β-effects.
10. Esmolol is an ultrashort-acting selective $\beta_1$-antagonist that reduces heart rate and, to a lesser extent, blood pressure.
11. Discontinuation of β-blocker therapy for 24–48 hr may trigger a withdrawal syndrome characterized by hypertension, tachycardia, and angina pectoris.

Adrenergic agonists and antagonists produce their clinical effects by interacting with the adrenergic receptors (ie, adrenoceptors). The clinical effects of these drugs can be deduced from an understanding of the adrenoceptor physiology and a knowledge of which receptors each drug activates or blocks.

# ADRENOCEPTOR PHYSIOLOGY

The term "adrenergic" originally referred to the effects of epinephrine (*adren*aline), although norepinephrine (noradrenaline) is the primary neurotransmitter responsible for most of the adrenergic activity of the sympathetic nervous system. With the exception of eccrine sweat glands and some blood vessels, norepinephrine is released by postganglionic sympathetic fibers at end-organ tissues (**Figure 14–1**). In contrast, acetylcholine is released by preganglionic sympathetic fibers and all parasympathetic fibers.

Norepinephrine is synthesized in the cytoplasm of sympathetic postganglionic nerve endings and stored in the vesicles (**Figure 14–2**). After release by a process of exocytosis, the action of norepinephrine is primarily terminated by reuptake into the postganglionic nerve ending (inhibited by tricyclic antidepressants), but also by diffusion from receptor sites, or via metabolism by monoamine oxidase (inhibited by monoamine oxidase inhibitors) and catechol-*O*-methyltransferase (**Figure 14–3**). Prolonged adrenergic activation leads to desensitization and hyporesponsiveness to further stimulation.

Adrenergic receptors are divided into two general categories: α and β. Each of these has been further subdivided into at least two subtypes: $\alpha_1$ and $\alpha_2$, and $\beta_1$, $\beta_2$, and $\beta_3$. The α-receptors have been further divided using molecular cloning techniques into $\alpha_{1A}$, $\alpha_{1B}$, $\alpha_{1D}$, $\alpha_{2A}$, $\alpha_{2B}$, and $\alpha_{2C}$. These receptors are linked to G proteins (**Figure 14–4**; Drs. Rodbell and Gilman received the Nobel Prize in physiology or medicine in 1994 for their discovery)—heterotrimeric receptors with α, β, and γ subunits. The different adrenoceptors are linked to specific G proteins, each with a unique effector, but each using guanosine triphosphate (GTP) as a cofactor. $\alpha_1$ is linked to $G_q$, which activates phospholipases; $\alpha_2$ is linked to $G_i$, which inhibits adenylate cyclase, and β is linked to $G_s$, which activates adenylate cyclase.

## $\alpha_1$-Receptors

$\alpha_1$-Receptors are postsynaptic adrenoceptors located in smooth muscle throughout the body (in the eye, lung, blood vessels, uterus, gut, and genitourinary system). Activation of these receptors increases intracellular calcium ion concentration, which leads to contraction of smooth muscles. Thus, $\alpha_1$-agonists are associated with mydriasis (pupillary dilation due to contraction of the radial eye muscles), bronchoconstriction, vasoconstriction, uterine contraction, and constriction of sphincters in the gastrointestinal and genitourinary tracts. $\alpha_1$-stimulation also inhibits insulin secretion and lipolysis. The myocardium possesses $\alpha_1$-receptors that have a positive inotropic effect, which might play a role in catecholamine-induced arrhythmia. During myocardial ischemia, enhanced $\alpha_1$-receptor coupling with agonists is observed. Nonetheless, the most important cardiovascular effect of $\alpha_1$-stimulation is vasoconstriction, which increases peripheral vascular resistance, left ventricular afterload, and arterial blood pressure.

## $\alpha_2$-Receptors

In contrast to $\alpha_1$-receptors, $\alpha_2$-receptors are located primarily on the presynaptic nerve terminals. Activation of these adrenoceptors inhibits adenylate cyclase activity. This decreases the entry of calcium ions into the neuronal terminal, which limits subsequent exocytosis of storage vesicles containing norepinephrine. Thus, $\alpha_2$-receptors create a negative feedback loop that inhibits further norepinephrine release from the neuron. In addition, vascular smooth muscle contains postsynaptic $\alpha_2$-receptors that produce vasoconstriction. More importantly, stimulation of postsynaptic $\alpha_2$-receptors in the central nervous system causes sedation and reduces sympathetic outflow, which leads to peripheral vasodilation and lower blood pressure.

## $\beta_1$-Receptors

β-Adrenergic receptors are classified into $\beta_1$, $\beta_2$, and $\beta_3$ receptors. The catecholamines, norepinephrine,

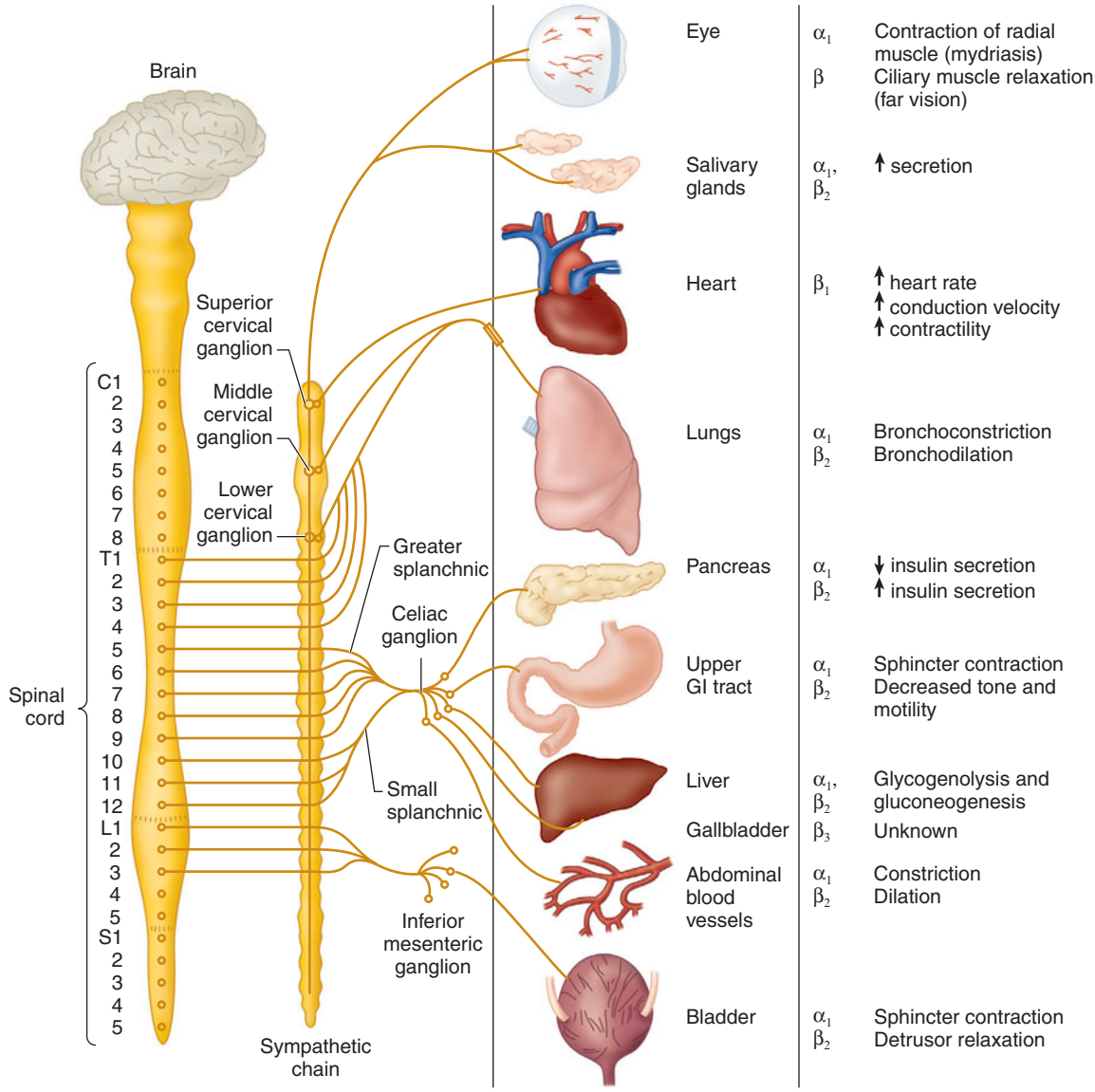


**FIGURE 14–1** The sympathetic nervous system. Organ innervation, receptor type, and response to stimulation. The origin of the sympathetic chain is the thoracoabdominal (T1–L3) spinal cord, in contrast to the craniosacral distribution of the parasympathetic nervous system. Another anatomic difference is the greater distance from the sympathetic ganglion to the visceral structures.

and epinephrine are equipotent on $\beta_1$ receptors, but epinephrine is significantly more potent than norepinephrine on $\beta_2$ receptors.

The most important $\beta_1$-receptors are located on the postsynaptic membranes in the heart. Stimulation of these receptors activates adenylate cyclase, which converts adenosine triphosphate to cyclic adenosine monophosphate and initiates a kinase phosphorylation cascade. Initiation of the cascade has positive chronotropic (increased heart

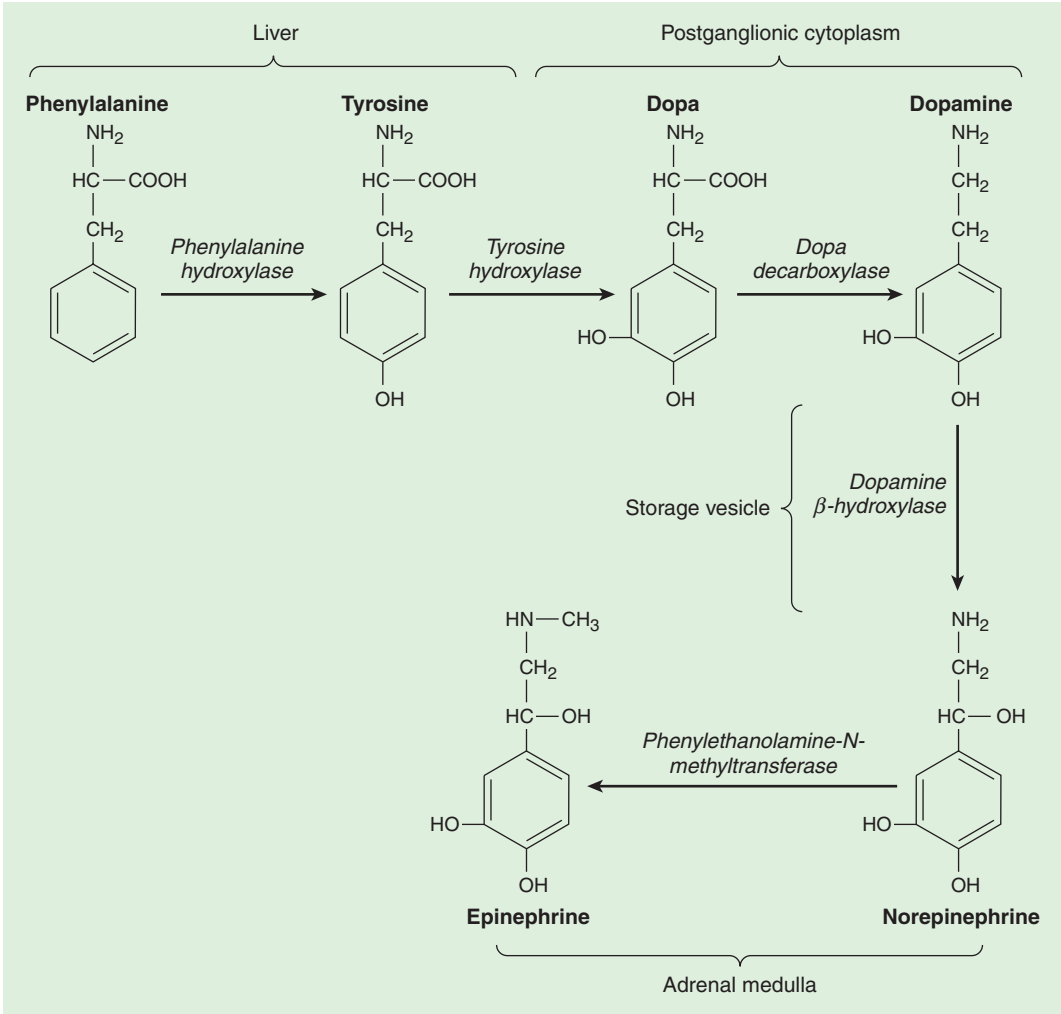


**FIGURE 14–2** The synthesis of norepinephrine. Hydroxylation of tyrosine to dopa is the rate-limiting step. Dopamine is actively transported into storage vesicles. Norepinephrine can be converted to epinephrine in the adrenal medulla.

rate), dromotropic (increased conduction), and inotropic (increased contractility) effects.

## $\beta_2$-Receptors

$\beta_2$-Receptors are primarily postsynaptic adrenoceptors located in smooth muscle and gland cells. They share a common mechanism of action with $\beta_1$-receptors: adenylate cyclase activation. Despite this commonality, $\beta_2$ stimulation relaxes smooth muscle, resulting in bronchodilation, vasodilation, and relaxation of the uterus (tocolysis), bladder, and gut. Glycogenolysis, lipolysis, gluconeogenesis, and insulin release are stimulated by $\beta_2$-receptor activation. $\beta_2$-agonists also activate the sodium–potassium pump, which drives potassium intracellularly and can induce hypokalemia and dysrhythmias.

## $\beta_3$-Receptors

$\beta_3$-Receptors are found in the gallbladder and brain adipose tissue. Their role in gallbladder physiology is unknown, but they are thought to play a role in lipolysis and thermogenesis in brown fat.

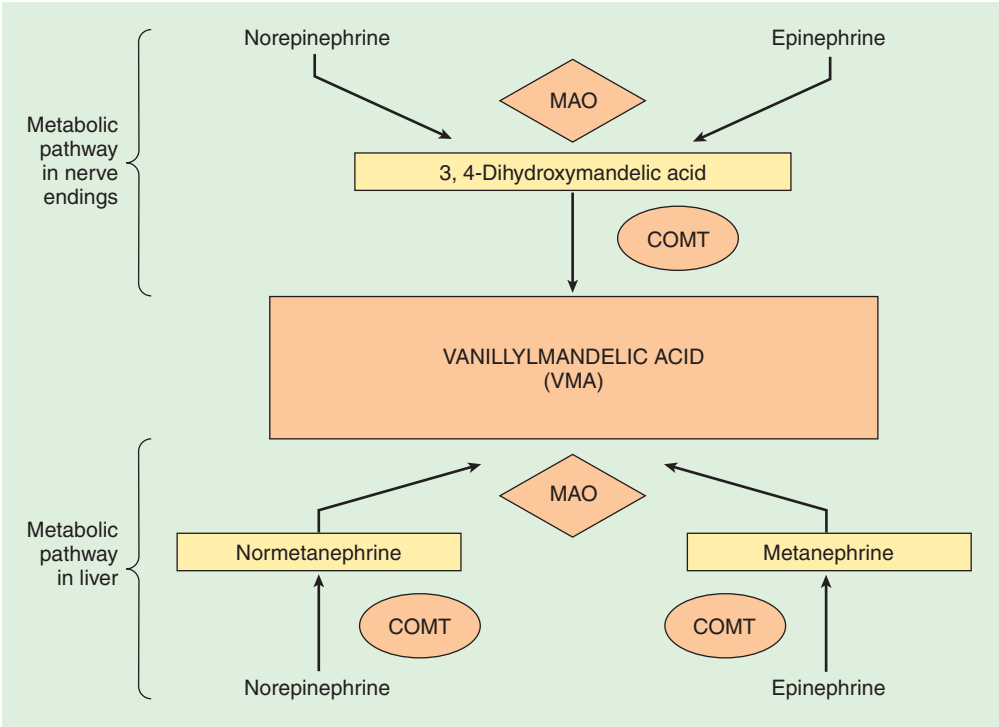


**FIGURE 14–3** Sequential metabolism of norepinephrine and epinephrine. Monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT) produce a common end product, vanillylmandelic acid (VMA).

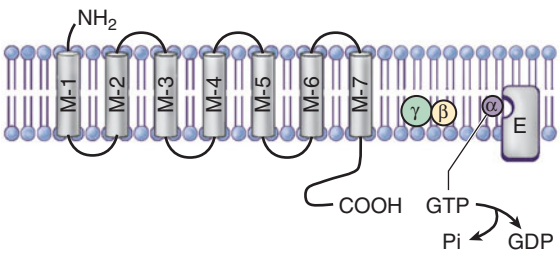


**FIGURE 14–4** The adrenoceptor is a transmembrane-spanning receptor made up of seven subunits, which is linked to a G protein. G proteins are trimeric endoplasmic membrane proteins made of α, β, and γ units. With activation, GTP on the α-subunit is replaced by GDP, stimulating a conformational change, disassociating the α, β, and γ units. Either the Gα or Gβγ subunits can activate (or inhibit) the enzyme effector for that adrenoceptor. M1–M7, membrane-spanning units; α, β, γ, subunits of G protein; GTP, guanosine triphosphate; $P_i$, inorganic phosphate—quickly assimilated; GDP, guanosine diphosphate; E, effector; cyclophosphatase for $G_q$, adenylate cyclase for $G_i$, and $G_s$.

## Dopaminergic Receptors

Dopamine (DA) receptors are a group of adrenergic receptors that are activated by dopamine; these receptors are classified as $D_1$ and $D_2$ receptors. Activation of $D_1$ receptors mediates vasodilation in the kidney, intestine, and heart. $D_2$ receptors are believed to play a role in the antiemetic action of droperidol.

# Adrenergic Agonists

Adrenergic agonists interact with varying specificity (selectivity) at α- and β-adrenoceptors (Tables 14–1 and 14–2).

Overlapping of activity complicates the prediction of clinical effects. For example, epinephrine stimulates $\alpha_1$-, $\alpha_2$-, $\beta_1$-, and $\beta_2$-adrenoceptors. Its net effect on arterial blood pressure depends on the balance between $\alpha_1$-vasoconstriction, $\alpha_2$- and

**TABLE 14–1 Receptor selectivity of adrenergic agonists.[1]**

| Drug | $\alpha_1$ | $\alpha_2$ | $\beta_1$ | $\beta_2$ | $DA_1$ | $DA_2$ |
|---|---|---|---|---|---|---|
| Phenylephrine | +++ | + | 0 | 0 | 0 | 0 |
| Methyldopa | + | + | 0 | 0 | 0 | 0 |
| Clonidine | + | ++ | 0 | 0 | 0 | 0 |
| Dexmedetomidine | + | +++ | 0 | 0 | 0 | 0 |
| Epinephrine[2] | ++ | ++ | +++ | ++ | 0 | 0 |
| Ephedrine[3] | ++ | ? | ++ | + | 0 | 0 |
| Fenoldopam | 0 | 0 | 0 | 0 | +++ | 0 |
| Norepinephrine[2] | ++ | ++ | ++ | 0 | 0 | 0 |
| Dopamine[2] | ++ | ++ | ++ | + | +++ | +++ |
| Dopexamine | 0 | 0 | + | +++ | ++ | +++ |
| Dobutamine | 0/+ | 0 | +++ | + | 0 | 0 |
| Terbutaline | 0 | 0 | + | +++ | 0 | 0 |

[1]0, no effect; +, agonist effect (mild, moderate, marked); ?, unknown effect; $DA_1$ and $DA_2$, dopaminergic receptors.
[2]The $\alpha_1$-effects of epinephrine, norepinephrine, and dopamine become more prominent at high doses.
[3]The primary mode of action of ephedrine is indirect stimulation.

$\beta_2$-vasodilation, and $\beta_1$-inotropic influences. Moreover, this balance changes at different doses.

1 Adrenergic agonists can be categorized as direct or indirect. Direct agonists bind to the receptor, whereas indirect agonists increase endogenous neurotransmitter activity. Mechanisms of indirect action include increased release or decreased reuptake of norepinephrine. The differentiation between direct and indirect mechanisms of action is particularly important in patients who

**TABLE 14–2 Effects of adrenergic agonists on organ systems.[1]**

| Drug | Heart Rate | Mean Arterial Pressure | Cardiac Output | Peripheral Vascular Resistance | Bronchodilation | Renal Blood Flow |
|---|---|---|---|---|---|---|
| Phenylephrine | ↓ | ↑↑↑ | ↓ | ↑↑↑ | 0 | ↓↓↓ |
| Epinephrine | ↑↑ | ↑ | ↑↑ | ↑/↓ | ↑↑ | ↓↓ |
| Ephedrine | ↑↑ | ↑↑ | ↑↑ | ↑ | ↑↑ | ↓↓ |
| Fenoldopam | ↑↑ | ↓↓↓ | ↓/↑ | ↓↓ | 0 | ↑↑↑ |
| Norepinephrine | ↓ | ↑↑↑ | ↓/↑ | ↑↑↑ | 0 | ↓↓↓ |
| Dopamine | ↑/↑↑ | ↑ | ↑↑↑ | ↑ | 0 | ↑↑↑ |
| Dopexamine | ↑/↑↑ | ↓/↑ | ↑↑ | ↑ | 0 | ↑ |
| Isoproterenol | ↑↑↑ | ↓ | ↑↑↑ | ↓↓ | ↑↑↑ | ↓/↑ |
| Dobutamine | ↑ | ↑ | ↑↑↑ | ↓ | 0 | ↑ |

[1]0, no effect; ↑, increase (mild, moderate, marked); ↓, decrease (mild, moderate, marked); ↓/↑, variable effect; ↑/↑↑, mild-to-moderate increase.

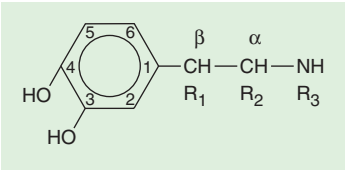


**FIGURE 14–5** Adrenergic agonists that have a 3,4-dihydroxybenzene structure are known as catecholamines. Substitutions at the $R_1$, $R_2$, and $R_3$ sites affect activity and selectivity.

have abnormal endogenous norepinephrine stores, as may occur with use of some antihypertensive medications or monoamine oxidase inhibitors. Intraoperative hypotension in these patients should be treated with direct agonists, as their response to indirect agonists will be altered.

Another feature distinguishing adrenergic agonists from each other is their chemical structure. Adrenergic agonists that have a 3,4-dihydroxybenzene structure (Figure 14–5) are known as catecholamines. These drugs are typically short-acting because of their metabolism by monoamine oxidase and catechol-*O*-methyltransferase. Patients taking monoamine oxidase inhibitors or tricyclic antidepressants may therefore demonstrate an exaggerated response to catecholamines. The naturally occurring catecholamines are epinephrine, norepinephrine, and DA. Changing the side-chain structure ($R_1$, $R_2$, $R_3$) of naturally occurring catecholamines has led to the development of synthetic catecholamines (eg, isoproterenol and dobutamine), which tend to be more receptor specific.

Adrenergic agonists commonly used in anesthesiology are discussed individually below. Note that the recommended doses for continuous infusion are expressed as mcg/kg/min for some agents and mcg/min for others. In either case, these recommendations should be regarded only as guidelines, as individual responses are quite variable.

# PHENYLEPHRINE

## Clinical Considerations

Phenylephrine is a noncatecholamine with predominantly selective $\alpha_1$-agonist activity. The primary effect of phenylephrine is peripheral vasoconstriction with a concomitant rise in systemic vascular resistance and arterial blood pressure. Reflex bradycardia mediated by the vagus nerve can reduce cardiac output. Phenylephrine is also used topically as a decongestant and a mydriatic agent.

## Dosing & Packaging

Small intravenous boluses of 50–100 µg (0.5–1 mcg/kg) of phenylephrine rapidly reverse reductions in blood pressure caused by peripheral vasodilation (eg, spinal anesthesia). The duration of action is short, lasting approximately 15 min after administration of a single dose. A continuous infusion (100 mcg/mL at a rate of 0.25–1 mcg/kg/min) will maintain arterial blood pressure, but at the expense of renal blood flow. Tachyphylaxis occurs with phenylephrine infusions requiring upward titration of the infusion. Phenylephrine must be diluted from a 1% solution (10 mg/1-mL ampule), usually to a 100 mcg/mL solution.

# $\alpha_2$-AGONISTS

## Clinical Considerations

Clonidine is an $\alpha_2$-agonist that is commonly used for its antihypertensive and negative chronotropic effects. More recently, it and other $\alpha_2$-agonists are increasingly being used for their sedative properties. Various studies have examined the anesthetic effects of oral (3–5 mcg/kg), intramuscular (2 mcg/kg), intravenous (1–3 mcg/kg), transdermal (0.1–0.3 mg released per day), intrathecal (75–150 mcg), and epidural (1–2 mcg/kg) clonidine administration. In general, clonidine seems to decrease anesthetic and analgesic requirements (decreases minimum alveolar concentration) and provides sedation and anxiolysis. During general anesthesia, clonidine reportedly enhances intraoperative circulatory stability by reducing catecholamine levels. During regional anesthesia, including peripheral nerve block, clonidine prolongs the duration of the block. Direct effects on the spinal cord may be mediated by $\alpha_2$-postsynaptic receptors within the dorsal horn. Other possible benefits include decreased postoperative shivering, inhibition of opioid-induced muscle rigidity, attenuation of opioid withdrawal symptoms, and the treatment of

some chronic pain syndromes. Side effects include bradycardia, hypotension, sedation, respiratory depression, and dry mouth.

4 Dexmedetomidine is a lipophylic α-methylol derivative with a higher affinity for $\alpha_2$-receptors than clonidine. Compared with clonidine, dexmedetomidine is more selective to $\alpha_2$-receptors ($\alpha_2$:$\alpha_1$ specificity ratio is 200:1 for clonidine and 1600:1 for dexmedetomidine). Dexmedetomidine has a shorter half-life (2–3 h) than clonidine (12–24 h). It has sedative, analgesic, and sympatholytic effects that blunt many of the cardiovascular responses seen during the perioperative period. The sedative and analgesic effects are mediated by $\alpha_2$-adrenergic receptors in the brain (locus ceruleus) and spinal cord. When used intraoperatively, dexmedetomidine reduces intravenous and volatile anesthetic requirements; when used postoperatively, it reduces concurrent analgesic and sedative requirements. Dexmedetomidine is useful in sedating patients in preparation for awake fiberoptic intubation. It is also a useful agent for sedating patients postoperatively in postanesthesia and intensive care units, because it does so without significant ventilatory depression. Rapid administration may elevate blood pressure, but hypotension and bradycardia can occur during ongoing therapy. The recommended dosing of dexmedetomidine consists of a loading dose at 1 mcg/kg over 10 min followed by an infusion at 0.2–0.7 mcg/kg/hr.

Although these agents are adrenergic agonists, they are also considered to be sympatholytic because

5 sympathetic outflow is reduced. Long-term use of these agents, particularly clonidine and dexmedetomidine, leads to supersensitization and up-regulation of receptors; with abrupt discontinuation of either drug, an acute withdrawal syndrome manifested by a hypertensive crisis can occur. Because of the increased affinity of dexmedetomidine for the $\alpha_2$-receptor, compared with that of clonidine, this syndrome may manifest after only 48 hr of dexmedetomidine use when the drug is discontinued.

### Dosing & Packaging

Clonidine is available as an oral, transdermal, or parenteral preparation. Dexmedetomidine is available as an injectable solution (100 mcg/mL), which should be diluted to 5–10 mcg/mL for bolus administration and titrated to effect.

## EPINEPHRINE

### Clinical Considerations

Epinephrine is an endogenous catecholamine synthesized in the adrenal medulla. Direct stimulation of $\beta_1$-receptors of the myocardium by epinephrine raises blood pressure, cardiac output, and myocardial oxygen demand by increasing contractility and heart rate (increased rate of spontaneous phase IV depolarization). $\alpha_1$-stimulation decreases splanchnic and renal blood flow but increases coronary perfusion pressure by increasing aortic diastolic pressure. Systolic blood pressure rises, although $\beta_2$-mediated vasodilation in skeletal muscle may lower diastolic pressure. $\beta_2$-stimulation also relaxes bronchial smooth muscle.

Administration of epinephrine is the principal pharmacological treatment for anaphylaxis and can be used to treat ventricular fibrillation. Complications include cerebral hemorrhage, coronary ischemia, and ventricular dysrhythmias. Volatile anesthetics, particularly halothane, potentiate the dysrhythmic effects of epinephrine.

### Dosing & Packaging

In emergency situations (eg, cardiac arrest and shock), epinephrine is administered as an intravenous bolus of 0.05–1 mg, depending on the severity of cardiovascular compromise. In major anaphylactic reactions, epinephrine should be used at a dose of 100–500 mcg (repeated, if necessary) followed by infusion. To improve myocardial contractility or heart rate, a continuous infusion is prepared (1 mg in 250 mL [4 mcg/mL]) and run at a rate of 2–20 mcg/min. Epinephrine is also used to reduce bleeding from the operative sites. Some local anesthetic solutions containing epinephrine at a concentration of 1:200,000 (5 mcg/mL) or 1:400,000 (2.5 mcg/mL) are characterized by less systemic absorption and a longer duration of action. Epinephrine is available in vials at a concentration of 1:1000 (1 mg/mL) and prefilled syringes at a concentration of 1:10,000 (0.1 mg/mL [100 mcg/mL]). A 1:100,000 (10 mcg/mL) concentration is available for pediatric use.

# EPHEDRINE

## Clinical Considerations

The cardiovascular effects of ephedrine, a noncatecholamine sympathomimetic, are similar to those of epinephrine: increase in blood pressure, heart rate, contractility, and cardiac output. Likewise, ephedrine is also a bronchodilator. There are important differences, however: ephedrine has a longer duration of action, is much less potent, has indirect and direct actions, and stimulates the central nervous system (it raises minimum alveolar concentration). The indirect agonist properties of ephedrine may be due to peripheral postsynaptic norepinephrine release, or by inhibition of norepinephrine reuptake.

6 Ephedrine is commonly used as a vasopressor during anesthesia. As such, its administration should be viewed as a temporizing measure while the cause of hypotension is determined and remedied. Unlike direct-acting $\alpha_1$-agonists, ephedrine is believed not to decrease uterine blood flow, and thus was regarded as the preferred vasopressor for most obstetric uses. Recently, however, phenylephrine has been argued to be a better vasopressor in obstetric patients undergoing neuroaxial anesthesia due its faster onset, shorter duration of action, and better titratability and maintenance of fetal pH. Ephedrine has also been reported to possess antiemetic properties, particularly in association with hypotension following spinal anesthesia. Clonidine premedication augments the effects of ephedrine.

## Dosing & Packaging

In adults, ephedrine is administered as a bolus of 2.5–10 mg; in children, it is given as a bolus of 0.1 mg/kg. Subsequent doses are increased to offset the development of tachyphylaxis, which is probably due to depletion of norepinephrine stores. Ephedrine is available in 1-mL ampules containing 25 or 50 mg of the agent.

# NOREPINEPHRINE

## Clinical Considerations

Direct $\alpha_1$-stimulation with little $\beta_2$-activity induces intense vasoconstriction of arterial and venous vessels. Increased myocardial contractility from $\beta_1$-effects, along with peripheral vasoconstriction, contributes to a rise in arterial blood pressure. Both systolic and diastolic pressures usually rise, but increased afterload and reflex bradycardia prevent any elevation in cardiac output. Decreased renal and splanchnic blood flow and increased myocardial oxygen requirements limit the outcome benefits of norepinephrine in the management of refractory shock. Norepinephrine has been used with an $\alpha$-blocker (eg, phentolamine) in an attempt to take advantage of its $\beta$-activity without the profound vasoconstriction caused by its $\alpha$-stimulation. Extravasation of norepinephrine at the site of intravenous administration can cause tissue necrosis.

## Dosing & Packaging

Norepinephrine is administered as a bolus (0.1 mcg/kg) or usually as a continuous infusion due to its short half-life at a rate of 2–20 mcg/min. Ampules contain 4 mg of norepinephrine in 4 mL of solution.

# DOPAMINE

## Clinical Considerations

The clinical effects of DA, an endogenous nonselective direct and indirect adrenergic and dopaminer-

7 gic agonist, vary markedly with the dose. At low doses (0.5–3 mcg/kg/min), DA primarily activates dopaminergic receptors (specifically, $DA_1$ receptors); stimulation of these receptors vasodilates the renal vasculature and promotes diuresis and natriuresis. Although this action increases renal blood flow, use of this "renal dose" does not impart any beneficial effect on renal function. When used in moderate doses (3–10 mcg/kg/min), $\beta_1$-stimulation increases myocardial contractility, heart rate, systolic blood pressure, and cardiac output. Myocardial oxygen demand typically increases more than supply. The $\alpha_1$-effects become prominent at higher doses (10–20 mcg/kg/min), causing an increase in peripheral vascular resistance and a fall in renal blood flow. The indirect effects of DA are due to release of norepinephrine from presynaptic sympathetic nerve ganglion.

DA is commonly used in the treatment of shock to improve cardiac output, support blood pressure, and maintain renal function. It is often used in combination with a vasodilator (eg, nitroglycerin

or nitroprusside), which reduces afterload and further improves cardiac output. The chronotropic and proarrhythmic effects of DA limit its usefulness in some patients.

### Dosing & Packaging

DA is administered as a continuous infusion at a rate of 1–20 mcg/kg/min. It is most commonly supplied in 5–10 mL vials containing 200 or 400 mg of DA.

## ISOPROTERENOL

Isoproterenol is of interest because it is a pure β-agonist. $\beta_1$-Effects increase heart rate, contractility, and cardiac output. Systolic blood pressure may increase or remain unchanged, but $\beta_2$-stimulation decreases peripheral vascular resistance and diastolic blood pressure. Myocardial oxygen demand increases while oxygen supply falls, making isoproterenol or any pure β-agonist a poor inotropic choice in most situations.

## DOBUTAMINE

### Clinical Considerations

Dobutamine is a racemic mixture of two isomers with affinity for both $\beta_1$ and $\beta_2$ receptors, with relatively higher selectivity for $\beta_1$ receptors. Its primary cardiovascular effect is a rise in cardiac output as a result of increased myocardial contractility. A decline in peripheral vascular resistance caused by $\beta_2$-activation usually prevents much of a rise in arterial blood pressure. Left ventricular filling pressure decreases, whereas coronary blood flow increases. 8 Favorable effects on myocardial oxygen balance are believed to make dobutamine a choice for patients with the combination of congestive heart failure and coronary artery disease, particularly if peripheral vascular resistance is elevated. However, because it has been shown to increase myocardial oxygen consumption, such as during stress testing (rationale for its use in perfusion imaging), some concern remains regarding its use in patients with myocardial ischemia. Moreover, dobutamine should not be routinely used without specific indications to facilitate separation from cardiopulmonary bypass.

### Dosing & Packaging

Dobutamine is administered as an infusion at a rate of 2–20 mcg/kg/min. It is supplied in 20-mL vials containing 250 mg.

## DOPEXAMINE

### Clinical Considerations

Dopexamine, a structural analogue of DA, has potential advantages over DA because it has less $\beta_1$-adrenergic (arrhythmogenic) and α-adrenergic effects. Because of the decreased β-adrenergic effects and its specific effect on renal perfusion, it may have advantages over dobutamine. The drug has been clinically available in many countries since 1990, but has not gained widespread acceptance in practice.

### Dosing & Packaging

Dopexamine infusion should be started at a rate of 0.5 mcg/kg/min, increasing to 1 mcg/kg/min at intervals of 10–15 min to a maximum infusion rate of 6 mcg/kg/min.

## FENOLDOPAM

### Clinical Considerations

Fenoldopam is a selective $D_1$-receptor agonist that has many of the benefits of DA but with little or no α- or β-adrenoceptor or $D_2$-receptor agonist activity. Fenoldopam has been shown to exert hypotensive effects characterized by a decrease in peripheral vascular resistance, along with an increase in renal blood flow, diuresis, and natriuresis. It is indicated for patients undergoing cardiac surgery and aortic aneurysm repair with potential risk of perioperative renal impairment. Fenoldopam exerts an antihypertensive effect, but helps to maintain renal blood flow. It is also indicated for patients who have severe hypertension, particularly those with renal impairment. Along with its recommended use in hypertensive emergencies, fenoldopam is also indicated in the prevention of contrast media-induced nephropathy. Fenoldopam has a fairly rapid onset of action and is easily titratable because of its short elimination half-life. The ability of fenoldopam to "protect" the kidney perioperatively remains the subject of ongoing studies.

### Dosing & Packaging

Fenoldopam is supplied in 1-, 2-, and 5-mL ampules, 10 mg/mL. It is started as a continuous infusion of 0.1 mcg/kg/min, increased by increments of 0.1 mcg/kg/min at 15- to 20-min intervals until target blood pressure is achieved. Lower doses have been associated with less reflex tachycardia.

## Adrenergic Antagonists

Adrenergic antagonists bind but do not activate adrenoceptors. They act by preventing adrenergic agonist activity. Like the agonists, the antagonists differ in their spectrum of receptor interaction.

## α-BLOCKERS—PHENTOLAMINE

### Clinical Considerations

Phentolamine produces a competitive (reversible) blockade of both $\alpha_1$- and $\alpha_2$- receptors. $\alpha_1$-Antagonism and direct smooth muscle relaxation are responsible for peripheral vasodilation and a decline in arterial blood pressure. The drop in blood pressure provokes reflex tachycardia. This tachycardia is augmented by antagonism of presynaptic $\alpha_2$-receptors in the heart because $\alpha_2$-blockade promotes norepinephrine release by eliminating negative feedback. These cardiovascular effects are usually apparent within 2 min and last up to 15 min. As with all of the adrenergic antagonists, the extent of the response to receptor blockade depends on the degree of existing sympathetic tone. Reflex tachycardia and postural hypotension limit the usefulness of phentolamine to the treatment of hypertension caused by excessive α-stimulation (eg, pheochromocytoma, clonidine withdrawal). Prazosin and phenoxybenzamine are examples of other alpha antagonists.

### Dosing & Packaging

Phentolamine is administered intravenously as intermittent boluses (1–5 mg in adults) or as a continuous infusion. To prevent tissue necrosis following extravasation of intravenous fluids containing an α-agonist (eg, norepinephrine), 5–10 mg of phentolamine in 10 mL of normal saline can be locally infiltrated. Phentolamine is packaged as a lyophilized powder (5 mg).

## MIXED ANTAGONISTS—LABETALOL

### Clinical Considerations

Labetalol blocks $\alpha_1$-, $\beta_1$-, and $\beta_2$-receptors. The ratio of α-blockade to β-blockade has been estimated to be approximately 1:7 following intravenous administration. This mixed blockade reduces peripheral vascular resistance and arterial blood pressure. Heart rate and cardiac output are usually slightly depressed or unchanged. Thus, labetalol lowers blood pressure without reflex tachycardia because of its combination of α- and β-effects, which is beneficial to patients with coronary artery disease. Peak effect usually occurs within 5 min after an intravenous dose. Left ventricular failure, paradoxical hypertension, and bronchospasm have been reported.

### Dosing & Packaging

The initial recommended dose of labetalol is 2.5–10 mg administered intravenously over 2 min. Twice this amount may be given at 10-min intervals until the desired blood pressure response is obtained. Labetalol can also be administered as a slow continuous infusion at a rate of 0.5–2 mg/min. However, due to its long elimination half-life (>5 h), prolonged infusions are not recommended.

## β-BLOCKERS

β-Receptor blockers have variable degrees of selectivity for the $\beta_1$-receptors. Those that are more $\beta_1$ selective have less influence on bronchopulmonary and vascular $\beta_2$-receptors (Table 14–3). Theoretically, a selective $\beta_1$-blocker would have less of an inhibitory effect on $\beta_2$-receptors and, therefore, might be preferred in patients with chronic obstructive lung disease or peripheral vascular disease. Patients with peripheral vascular disease could potentially have a decrease in blood flow if $\beta_2$-receptors, which dilate the arterioles, are blocked. β-Receptor blocking agents also reduce intraocular pressure in patients with glaucoma.

**TABLE 14–3 Pharmacology of β-blockers.[1]**

| | Selectivity for $\beta_1$-Receptors | ISA | α-Blockade | Hepatic Metabolism | $t_{1/2}$ |
|---|---|---|---|---|---|
| Atenolol | + | 0 | 0 | 0 | 6–7 |
| Esmolol | + | 0 | 0 | 0 | –¼ |
| Labetalol | | 0 | + | + | 4 |
| Metoprolol | + | 0 | 0 | + | 3–4 |
| Propranolol | | 0 | 0 | + | 4–6 |

[1]ISA, intrinsic sympathomimetic activity; +, mild effect; 0, no effect.

β-Blockers are also classified by the amount of intrinsic sympathomimetic activity (ISA) they have. Many of the β-blockers have some agonist activity; although they would not produce effects similar to full agonists (such as epinephrine), β-blockers with ISA may not be as beneficial as β-blockers without ISA in treating patients with cardiovascular disease.

β-Blockers can be further classified as those that are eliminated by hepatic metabolism (such as metoprolol), those that are excreted by the kidneys unchanged (such as atenolol), or those that are hydrolyzed in the blood (such as esmolol).

# ESMOLOL

## Clinical Considerations

10 Esmolol is an ultrashort-acting selective $\beta_1$-antagonist that reduces heart rate and, to a lesser extent, blood pressure. It has been successfully used to prevent tachycardia and hypertension in response to perioperative stimuli, such as intubation, surgical stimulation, and emergence. For example, esmolol (0.5–1 mg/kg) attenuates the rise in blood pressure and heart rate that usually accompanies electroconvulsive therapy, without significantly affecting seizure duration. Esmolol is as effective as propranolol in controlling the ventricular rate of patients with atrial fibrillation or flutter. Although esmolol is considered to be cardioselective, at higher doses it inhibits $\beta_2$-receptors in bronchial and vascular smooth muscle.

The short duration of action of esmolol is due to rapid redistribution (distribution half-life is 2 min) and hydrolysis by red blood cell esterase (elimination half-life is 9 min). Side effects can be reversed within minutes by discontinuing its infusion. As with all $\beta_1$-antagonists, esmolol should be avoided in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock, or overt heart failure.

## Dosing & Packaging

Esmolol is administered as a bolus (0.2–0.5 mg/kg) for short-term therapy, such as attenuating the cardiovascular response to laryngoscopy and intubation. Long-term treatment is typically initiated with a loading dose of 0.5 mg/kg administered over 1 min, followed by a continuous infusion of 50 mcg/kg/min to maintain therapeutic effect. If this fails to produce a sufficient response within 5 min, the loading dose may be repeated and the infusion increased by increments of 50 mcg/kg/min every 5 min to a maximum of 200 mcg/kg/min.

Esmolol is supplied as multidose vials for bolus administration containing 10 mL of drug (10 mg/mL). Ampules for continuous infusion (2.5 g in 10 mL) are also available but must be diluted prior to administration to a concentration of 10 mg/mL.

# METOPROLOL

## Clinical Considerations

Metoprolol is a selective $\beta_1$-antagonist with no intrinsic sympathomimetic activity. It is available for both oral and intravenous use. It can be administered intravenously in 2–5 mg increments every 2 to 5 min, titrated to blood pressure and heart rate.

# PROPRANOLOL

## Clinical Considerations

Propranolol nonselectively blocks $\beta_1$- and $\beta_2$-receptors. Arterial blood pressure is lowered by several mechanisms, including decreased myocardial contractility, lowered heart rate, and diminished renin release. Cardiac output and myocardial oxygen demand are reduced. Propranolol is particularly useful during myocardial ischemia related to increased blood pressure and heart rate. Impedance of ventricular ejection is beneficial in patients with obstructive cardiomyopathy and aortic aneurysm. Propranolol slows atrioventricular conduction and stabilizes myocardial membranes, although the latter effect may not be significant at clinical doses. Propranolol is particularly effective in slowing the ventricular response to supraventricular tachycardia, and it occasionally controls recurrent ventricular tachycardia or fibrillation caused by myocardial ischemia. Propranolol blocks the β-adrenergic effects of thyrotoxicosis and pheochromocytoma.

Side effects of propranolol include bronchospasm ($\beta_2$-antagonism), congestive heart failure, bradycardia, and atrioventricular heart block ($\beta_1$-antagonism). Propranolol may worsen the myocardial depression of volatile anesthetics (eg, halothane) or unmask the negative inotropic characteristics of indirect cardiac stimulants (eg, isoflurane). Concomitant administration of propranolol and verapamil (a calcium channel blocker) can synergistically depress heart rate, contractility, and atrioventricular node conduction.

Propranolol is extensively protein bound and is cleared by hepatic metabolism. Its elimination half-life of 100 min is quite long compared with that of esmolol.

## Dosing & Packaging

Individual dosage requirements of propranolol depend on baseline sympathetic tone. Generally, propranolol is titrated to the desired effect, beginning with 0.5 mg and progressing by 0.5-mg increments every 3–5 min. Total doses rarely exceed 0.15 mg/kg. Propranolol is supplied in 1-mL ampules containing 1 mg.

# NEBIVOLOL

## Clinical Considerations

Nebivolol is a newer generation β-blocker with high affinity for $\beta_1$-receptors. The drug is unique in its ability to cause direct vasodilation via its stimulatory effect on endothelial nitric oxide synthase. It is presently available only in oral formulation; the recommended dose is 5–40 mg daily.

# CARVEDILOL

Carvedilol is a mixed β- and α-blocker used in the management of chronic heart failure secondary to cardiomyopathy, left ventricular dysfunction following acute myocardial infarction, and hypertension. Carvedilol dosage is individualized and gradually increased up to 25 mg twice daily, as required and tolerated.

# PERIOPERATIVE β-BLOCKER THERAPY

Management of β-blockers perioperatively is a key anesthesia performance indicator and is closely monitored by various "quality management" agencies. Although studies regarding the perioperative administration of β-blockers have yielded conflicting results as to benefit, maintenance of β-blockers in patients already being treated with them is essential, unless contraindicated by other clinical concerns.

β-Blocker therapy in the perioperative period has the potential to reduce the perioperative cardiovascular complications (myocardial ischemia, stroke, cardiac failure) due to counteraction of catecholamine-induced tachycardia and hypertension. However, these beneficial effects have not been widely demonstrated in recent clinical trials. Perioperative β-blocker therapy was associated with a reduced risk of in-hospital death in a small group of high-risk patients (ie, those with a Revised Cardiac Score Index of 3 or higher), but showed no improvement or even an increase in stroke and overall mortality in low-risk patients undergoing noncardiac surgery.

Current American Heart Association/American College of Cardiology guidelines recommend continuation of β-blocker therapy during the

perioperative period in patients who are receiving β-blockers for the treatment of angina, symptomatic arrhythmia, heart failure, and hypertension. In addition, β-blocker therapy should be initiated in patients undergoing vascular surgery who are at high risk of cardiac events because of findings of myocardial ischemia during perioperative testing. The guidelines also note that β-blockers titrated to heart rate and blood pressure are "reasonable" in patients undergoing vascular surgery who have more than one cardiac risk factor. Additionally, the guidelines suggest that perioperative β-blockers are likewise "reasonable" in patients undergoing intermediate-risk procedures who have more than one cardiac disease risk factor. The routine administration of high-dose β-blockers in the absence of dose titration may be harmful in patients not currently taking β-blockers who are undergoing noncardiac surgery.

11 Discontinuation of β-blocker therapy for 24–48 hr may trigger a withdrawal syndrome characterized by hypertension (rebound hypertension), tachycardia, and angina pectoris. This effect seems to be caused by an increase in the number of β-adrenergic receptors (up-regulation).

## CASE DISCUSSION

### Pheochromocytoma

**A 45-year-old man with a history of paroxysmal attacks of headache, hypertension, sweating, and palpitations is scheduled for resection of an abdominal pheochromocytoma.**

***What is a pheochromocytoma?***

A pheochromocytoma is a vascular tumor of chromaffin tissue (most commonly the adrenal medulla) that produces and secretes norepinephrine and epinephrine. The diagnosis and management of pheochromocytoma are based on the effects of abnormally high circulating levels of these endogenous adrenergic agonists.

***How is the diagnosis of pheochromocytoma made in the laboratory?***

Urinary excretion of vanillylmandelic acid (an end product of catecholamine metabolism), norepinephrine, and epinephrine is often markedly increased. Elevated levels of urinary catecholamines and metanephrines (Figure 14–3) provide a highly accurate diagnosis. Fractionated plasma-free metanephrine levels may be superior to urinary studies in making the diagnosis. The location of the tumor can be determined by magnetic resonance imaging or computed tomographic scan with or without contrast.

***What pathophysiology is associated with chronic elevations of norepinephrine and epinephrine?***

$\alpha_1$-Stimulation increases peripheral vascular resistance and arterial blood pressure. Hypertension can lead to intravascular volume depletion (increasing hematocrit), renal failure, and cerebral hemorrhage. Elevated peripheral vascular resistance also increases myocardial work, which predisposes patients to myocardial ischemia, ventricular hypertrophy, and congestive heart failure. Prolonged exposure to epinephrine and norepinephrine may lead to a catecholamine-induced cardiomyopathy. Hyperglycemia results from decreased insulin secretion in the face of increased glycogenolysis and gluconeogenesis. $\beta_1$-Stimulation increases automaticity and ventricular ectopy.

***Which adrenergic antagonists might be helpful in controlling the effects of norepinephrine and epinephrine hypersecretion?***

Phenoxybenzamine, an $\alpha_1$-antagonist, effectively reverses the vasoconstriction, resulting in a drop in arterial blood pressure and an increase in intravascular volume (hematocrit drops). Glucose intolerance is often corrected. Phenoxybenzamine can be administered orally and is longer acting than phentolamine, another $\alpha_1$-antagonist. For these reasons, phenoxybenzamine is often administered preoperatively to control symptoms.

Intravenous phentolamine is often used intraoperatively to control hypertensive episodes. Compared with some other hypotensive agents, however, phentolamine has a slow onset and long duration of action; furthermore, tachyphylaxis often develops.

$\beta_1$-Blockade with an agent such as labetalol is recommended for patients with tachycardia or ventricular arrhythmias.

***Why should $\alpha_1$-receptors be blocked with phenoxybenzamine before administration of a $\beta$-antagonist?***

If β-receptors are blocked first, norepinephrine and epinephrine will produce unopposed α-stimulation. $\beta_2$-Mediated vasodilation will not be able to offset $\alpha_1$-vasoconstriction, and peripheral vascular resistance would increase. This may explain the paradoxical hypertension that has been reported in a few patients with pheochromocytoma treated only with labetalol. Finally, the myocardium might not be able to handle its already elevated workload without the inotropic effects of $\beta_1$-stimulation.

***Which anesthetic agents should be specifically avoided?***

Succinylcholine-induced fasciculations of the abdominal musculature will increase intraabdominal pressure, which theoretically might cause release of catecholamines from the tumor. Ketamine is a sympathomimetic and would exacerbate the effects of adrenergic agonists. Halothane sensitizes the myocardium to the arrhythmogenic effects of epinephrine. Vagolytic drugs (eg, anticholinergics and pancuronium) will worsen the imbalance of autonomic tone. Because histamine provokes catecholamine secretion by the tumor, drugs associated with histamine release (eg, atracurium) are best avoided. Vecuronium and rocuronium are probably the neuromuscular blocking agents of choice.

***Would an epidural or spinal technique effectively block sympathetic hyperactivity?***

A major regional block—such as an epidural or spinal anesthetic—could block sensory (afferent) nerves and sympathetic (efferent) discharge in the area of the surgical field. The catecholamines released from a pheochromocytoma during surgical manipulation would still be able to bind and activate adrenergic receptors throughout the body, however.

## GUIDELINES

Fleisher LA, Beckman JA, Brown KA, et al: 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. Circulation 2009;120:2123.

## SUGGESTED READING

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