

CHAPTER 15 ■ AUTONOMIC NERVOUS SYSTEM

Anesthesiology is the practice of autonomic nervous system (ANS) medicine (Johnson JO, Grecu L, Lawson NW: Autonomic nervous system. In *Clinical Anesthesia*. Edited by Barash PG, Cullen BF, Stoelting RK, Cahalan MK, Stock MC. Philadelphia: Lippincott Williams & Wilkins, 2009, pp 326–368). Data recorded on the anesthesia record often reflect ANS function and homeostasis. Drugs used during anesthesia as well as painful stimulation and disease states frequently produce ANS-related side effects.

I. FUNCTIONAL ANATOMY

The ANS is divided into the sympathetic nervous system (SNS; adrenergic system) and the parasympathetic nervous system (PNS; cholinergic system) (Fig. 15-1). The SNS and PNS produce complementary effects on the activity of various organ systems (Table 15-1).

A. Central Autonomic Organization. The principal site of ANS integration (blood pressure control, temperature regulation, stress responses) is the hypothalamus. Vital centers for hemodynamic and ventilatory control are located in the medulla oblongata and pons. ANS hyperreflexia is an example of spinal cord mediation of ANS reflexes without integration of function from higher inhibitory centers.

B. Peripheral Autonomic Nervous System Organization (Fig. 15-2)

1. The cell body of the preganglionic neuron originates in the central nervous system (CNS) and synapses in an autonomic ganglion. (The adrenal medulla is an exception.) Preganglionic fibers are myelinated (rapid conducting).

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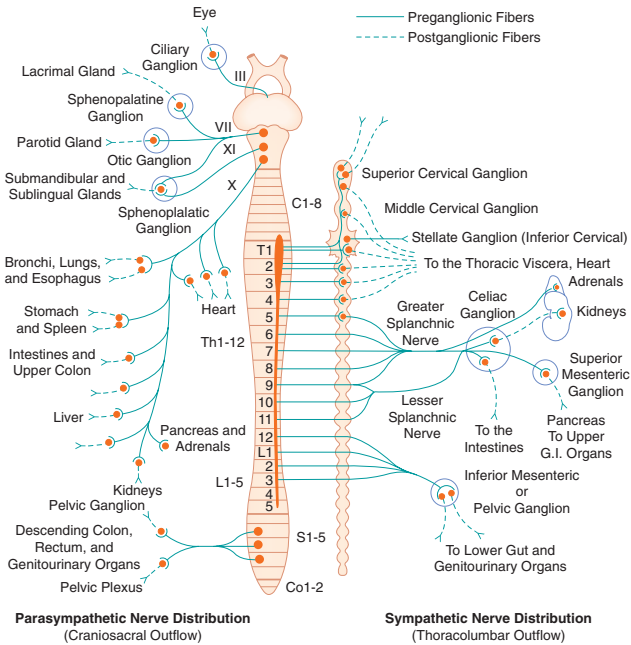


FIGURE 15-1. Schematic distribution of the craniosacral (parasympathetic) and thoracolumbar (sympathetic) nervous systems. Parasympathetic preganglionic fibers pass directly to the organ that is innervated (with discrete and limited effects). Activation of the sympathetic fibers produces a more diffuse physiologic response. GI = gastrointestinal.

2. Postganglionic neurons arise from the autonomic ganglia and are distributed to effector organs. Postganglionic fibers are unmyelinated (slow conducting).
 - a. The 22 pairs of SNS (paravertebral) ganglia are located closer to the spinal cord than to the innervated organ.
 - b. The PNS ganglia are located in or near the innervated organ.
3. Whereas activation of the SNS produces a diffuse physiologic response (mass reflex), activation of the PNS produces more discrete responses. For example, vagal stimulation may produce bradycardia with no effect on intestinal motility.

178 *Anatomy and Physiology***TABLE 15-1****HOMEOSTATIC BALANCE BETWEEN DIVISIONS OF THE AUTONOMIC NERVOUS SYSTEM**

	Sympathetic Nervous System	Parasympathetic Nervous System
Heart		
Sinoatrial node	Tachycardia	Bradycardia
Atrioventricular node	Increased conduction	Decreased conduction
His-Purkinje system	Increased automaticity Increased conduction velocity	Minimal effect
Myocardium	Increased contractility Increased conduction velocity Increased automaticity	Minimal decrease in contractility
Coronary vessels	Constriction (α_1) Dilation (β_1)	
Blood Vessels		
Skin and mucosa	Constriction	Dilation
Skeletal muscle	Constriction (α_1) > dilation (β)	Dilation
Pulmonary	Constriction	Dilation
Bronchial Smooth Muscle	Relaxation	Contraction
Gastrointestinal Tract		
Gallbladder	Relaxation	Contraction
Gut motility and secretions	Decreased	Increased
Bladder		
Detrusor	Relaxation	Contraction
Trigone	Contraction	Relaxation
Glands (nasal, lacrimal, salivary, pancreatic)	Vasoconstriction and reduced secretion	Stimulation of secretions
Sweat Glands	Diaphoresis (cholinergic)	No effect
Apocrine Glands	Thick and odiferous secretions	No effect
Eyes		
Pupil	Mydriasis	Miosis
Ciliary	Relaxation for far vision	Contraction for near vision

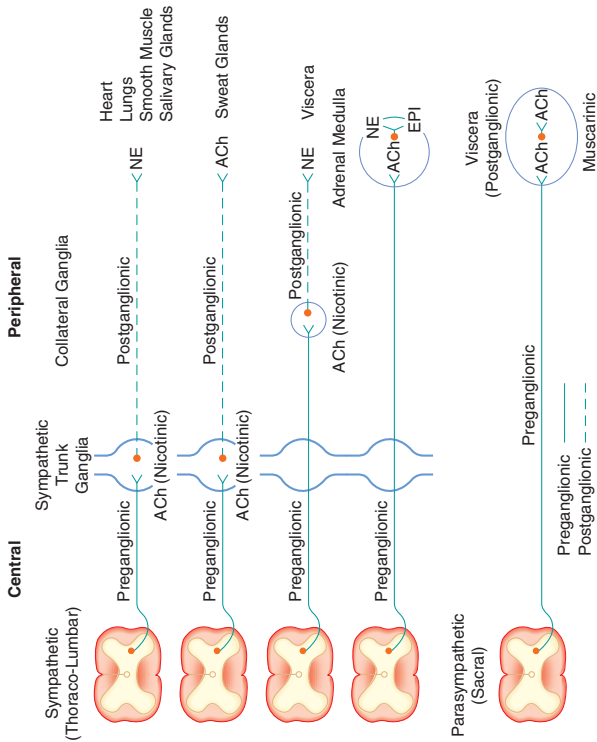


FIGURE 15-2. Schematic diagram of the efferent autonomic nervous system. Ach = acetylcholine.

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C. Autonomic Innervation

1. **Heart.** SNS and PNS innervation of the heart (via the stellate ganglion) influences heart rate (chronotropism), strength of contraction (inotropism), and coronary blood flow.
 - a. The PNS cardiac vagal fibers are distributed mainly to the sinoatrial (SA) and atrioventricular (AV) nodes, such that the main effect of cardiac vagal stimulation is chronotropic. (Strong vagal stimulation can arrest SA node firing and block impulse conduction to the ventricles.)
 - b. The SNS has the same supraventricular distribution as the PNS but with stronger distribution to the ventricles. (Normal SNS tone maintains contractility about 20% above that in the absence of SNS stimulation.)
2. **Peripheral circulation.** The SNS is the most important regulator of the peripheral circulation. Basal ANS tone maintains arteriolar diameter at about 50% of maximum, thus permitting the potential for further vasoconstriction or vasodilation. By functioning as a reservoir for about 80% of the blood volume, small changes in venous capacitance produced by SNS-mediated venoconstriction produce large changes in venous return.

II. AUTONOMIC NERVOUS SYSTEM TRANSMISSION

- A. Transmission of impulses across the nerve terminal junctional sites (synaptic cleft) of the peripheral ANS occurs through the mediation of liberated chemicals (neurotransmitters). These neurotransmitters interact with a receptor on the end organ to evoke a biologic response.
- B. **Parasympathetic Nervous System Neurotransmission**
 1. **Acetylcholine (ACh)** is the neurotransmitter at preganglionic nerve endings of the SNS and PNS and at postganglionic nerve endings of the PNS.
 2. The ability of a receptor to modulate the function of an effector organ depends on rapid recovery to its baseline state after stimulation. ACh removal occurs by rapid hydrolysis by acetylcholinesterase (true cholinesterase). Pseudocholinesterase (plasma

cholinesterase) is not physiologically significant in the termination (hydrolysis) of ACh action.

C. Sympathetic Nervous System Neurotransmission

1. Norepinephrine is the neurotransmitter at postganglionic nerve endings of the SNS (except in the sweat glands, where ACh is the neurotransmitter).
 - a. Adenosine triphosphate (ATP) is released with norepinephrine and thus functions as a co-neurotransmitter.
 - b. Epinephrine is the principal hormone released by chromaffin cells (which function as postganglionic SNS neurons) into the circulation to function as a neurotransmitter hormone.
2. **Catecholamines: The First Messenger**
 - a. Endogenous catecholamines are dopamine (neurotransmitter in the CNS), norepinephrine, and epinephrine. A catecholamine (including synthetic catecholamines) is any compound with a catechol nucleus (benzene ring with two adjacent hydroxyl groups) and an amine-containing side chain (Fig. 15-3).
 - b. The effects of endogenous or synthetic catecholamines on adrenergic receptors can be indirect (little intrinsic activity but stimulate release of stored neurotransmitter) and direct.
3. **Inactivation** of catecholamines is by reuptake back into presynaptic nerve terminals by extraneuronal uptake, diffusion, and metabolism.

III. RECEPTORS

Receptors appear to be protein macromolecules on cell membranes, which when activated by an agonist (ACh or norepinephrine) lead to a response by an effector cell. An antagonist is a substance that attaches to the receptor (prevents access of an agonist) but does not elicit a response by the effector cell.

- A. Cholinergic receptors** are subdivided into muscarinic (postganglionic nerve endings) and nicotinic (autonomic ganglia, neuromuscular junction) receptors. ACh is the neurotransmitter at cholinergic receptors. Atropine is a specific antagonist at muscarinic receptors.

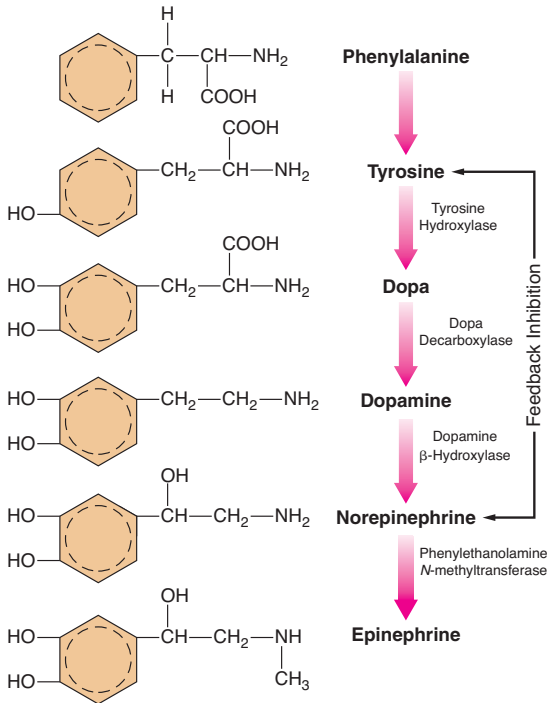
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FIGURE 15-3. Synthesis of catecholamines.

B. Adrenergic receptors are subdivided into α , β , and dopaminergic, with subtypes for each category (Table 15-2).

1. α -Adrenergic Receptors in the Cardiovascular System

- Coronary arteries.** Postsynaptic α_2 receptors predominate in the large epicardial conductance vessels. (They contribute about 5% to total coronary artery resistance, which is why phenylephrine has little influence on resistance to blood flow in coronary arteries.) Postsynaptic α_2 receptors predominate in small coronary artery resistance vessels. The density of α_2 receptors in the coronary arteries increases in response to myocardial ischemia.

TABLE 15-2
ADRENERGIC RECEPTORS AND ORDER OF POTENCY OF AGONISTS AND ANTAGONISTS

Receptor	Potency	Agonists	Antagonists	Location	Action
α_1	+++	Norepinephrine	Phenylephrine	Smooth muscle (vascular, iris, radial, pilomotor, uterus, trigone, GI and bladder sphincters) Brain Smooth muscle (GI) Heart Adrenergic nerve endings	Contraction Vasoconstriction
	+++	Epinephrine	Phentolamine*		
	++	Dopamine	Ergot alkaloids*		
	++	Isoproterenol	Prazosin		
	+		Tolazoline* Labetalol*		
α_2	+++	Clonidine	Yohimbine	Presynaptic (CNS) Platelets Adipose tissue Endocrine pancreas Kidney Brain	Neurotransmission Relaxation Glycogenolysis Inhibition of norepinephrine release Aggregation Granule release Inhibition of lipolysis Inhibition of insulin release Inhibition of renin release Neurotransmission
	++	Norepinephrine	Piperoxan		
	++	Epinephrine	Phentolamine*		
	++	Norepinephrine	Phenylephrine		
	+	Phenylephrine	Tolazoline* Labetalol*		

(continued)

TABLE 15-2
ADRENERGIC RECEPTORS AND ORDER OF POTENCY OF AGONISTS AND ANTAGONISTS (Continued)

Receptor	Potency	Agonists	Antagonists	Location	Action
β_1	+++	Isoproterenol*	Acebutolol	Heart	Increased heart rate Increased contractility Increased conduction velocity
	++	Epinephrine Norepinephrine	Practolol Propranolol*		Coronary vasodilation
	+	Dopamine	Alprenolol* Metoprolol Esmolol Propranolol*	Adipose tissue	Lipolysis
β_2	+++	Isoproterenol		Liver	Glycogenolysis Gluconeogenesis
	++	Epinephrine Norepinephrine	Butoxamine Alprenolol Esmolol		
	+	Dopamine		Skeletal muscle	Glycogenolysis Lactate release
Dopamine ₁	+++	Fenoldopam	Nadolol Timolol Labetalol	Smooth muscle	Relaxation
	++	Dopamine		Vascular smooth muscle	Vasodilation
	+	Epinephrine Metoclopramide	Haloperidol Droperidol Phenothiazines	Renal Mesentery	
Dopamine ₂	++	Dopamine	Domperidone	Presynaptic-adrenergic nerve endings	Inhibition of norepinephrine release
	+	Bromocriptine			

*Nonspecific.
CNS = central nervous system; GI = gastrointestinal.

- b. Peripheral Vessels.** Presynaptic α_2 -vascular receptors mediate vasodilation, and postsynaptic α_1 - and α_2 -vascular receptors mediate vasoconstriction. Postsynaptic α_2 -vascular receptors predominate on the venous side of the circulation. Actions attributed to postsynaptic α_2 receptors include arterial and venous vasoconstriction, platelet aggregation, inhibition of insulin release, inhibition of bowel motility, and inhibition of antidiuretic hormone release.
- 2. α Receptors in the Kidneys.** The α_1 receptors dominate in the renal vasculature (vasoconstriction modulates renal blood flow), and the α_2 receptors predominate in the renal tubules, especially the loops of Henle (which stimulate water and sodium excretion).
- 3. β Receptors in the Cardiovascular System**
- a. Myocardium.** Postsynaptic β_1 receptors and presynaptic β_2 receptors probably play similar roles in the regulation of heart rate and myocardial contractility. Increased circulating catecholamine levels associated with congestive heart failure result in down-regulation of β_1 receptors with relative sparing of β_2 and α_1 receptors. (β_2 and α_1 receptors increasingly mediate the inotropic response to catecholamines during cardiac failure.)
- b. Peripheral Vessels.** Postsynaptic vascular β receptors are predominantly β_2 .
- 4. β Receptors in the Kidneys.** β_1 receptors are more prominent than β receptors in the kidneys, and their activation results in renin release.
- C. Adrenergic Receptor Numbers and Sensitivity**
- 1.** Receptors are dynamically regulated by a variety of conditions (ambient concentrations of catecholamines and drugs and genetic factors), resulting in altered responses to catecholamines and ANS stimulation.
- 2.** Alteration in the number or density of receptors is referred to as up-regulation or down-regulation. Chronic treatment with clonidine or propranolol results in up-regulation and a withdrawal syndrome if the drug is acutely discontinued.

IV. AUTONOMIC NERVOUS SYSTEM REFLEXES AND INTERACTIONS

The ANS has been compared to a computer circuit (sensor, afferent pathway, CNS integration, efferent pathway).

- A. **Baroreceptors** located in the carotid sinus and aortic arch react to alterations in stretch caused by changes in blood pressure (Fig. 15-4). Volatile anesthetics interfere with baroreceptor function; thus, anesthetic-induced decreases in blood pressure may not evoke changes in heart rate. Compliance of stretch receptors and their sensitivity may be altered by carotid sinus atherosclerosis. (Carotid artery disease may be a source of hypertension rather than a result.)
- B. **Venous baroreceptors** located in the right atrium and great veins produce an increased heart rate when the right atrium is stretched by increased filling pressure

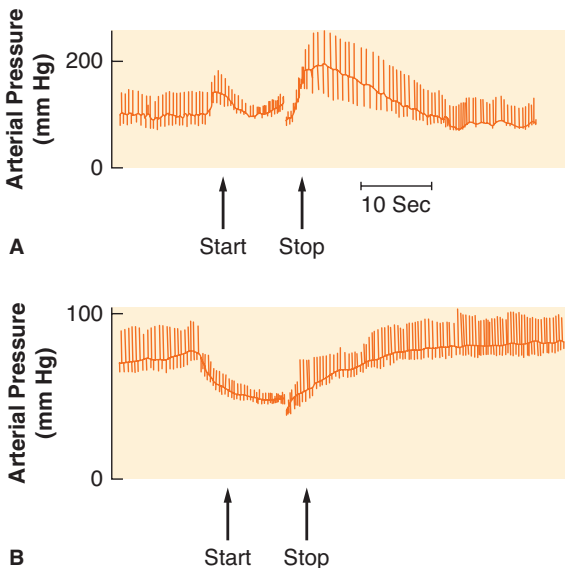


FIGURE 15-4. Blood pressure and heart rate response to a Valsalva maneuver (A, normal; B, abnormal in a patient with cervical quadriplegia).

(Bainbridge reflex). Slowing of the heart rate during spinal anesthesia may reflect activation of venous baroreceptors as a result of decreased venous return.

V. CLINICAL AUTONOMIC NERVOUS SYSTEM PHARMACOLOGY

Drugs that modify ANS activity can be classified by their site of action and the mechanism of action or pathology (antihypertensives) for which they are administered.

A. Cholinergic Drugs. Muscarinic agonists act at sites in the body where ACh is the neurotransmitter.

1. **Indirect Cholinomimetics.** Anticholinesterases (neostigmine, pyridostigmine, edrophonium) inhibit activity of acetylcholinesterase, which normally destroys ACh by hydrolysis. As a result of this inhibition, ACh accumulates at muscarinic and nicotinic receptors. Simultaneous administration of an anticholinergic drug protects patients against undesired muscarinic effects (bradycardia, salivation, bronchospasm, intestinal hypermotility) without preventing the nicotinic effects of ACh (reversal of nondepolarizing muscle relaxants).

B. Cholinergic Drugs. Muscarinic antagonist refers to a specific drug action for which the term *anticholinergic* is often used (any drug that interferes with the action of ACh as a transmitter). Anticholinergic drugs (atropine, scopolamine, glycopyrrolate) interfere with the muscarinic actions of ACh by competitive inhibition of cholinergic postganglionic nerves.

1. There are marked variations in sensitivity to anticholinergic drugs at different muscarinic sites.
2. **Central anticholinergic syndrome** is characterized by symptoms that range from sedation to delirium, presumably reflecting inhibition of muscarinic receptors in the CNS by anticholinergics (this is unlikely with glycopyrrolate, which cannot easily cross the blood–brain barrier). Treatment is with physostigmine. Its tertiary amine structure allows it to cross the blood–brain barrier rapidly; other anticholinesterases are quaternary ammonium compounds that lack the lipid solubility necessary to gain prompt entrance into the CNS.

C. Sympathomimetic Drugs. Catecholamines and sympathomimetic drugs continue to be the pharmacologic

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mainstay of cardiovascular support for the low-flow state (Table 15-3). It is necessary to become familiar with only a few drugs to manage most clinical situations (Table 15-4). **Low-output syndrome** is present when an individual has abnormalities of the heart, blood volume, or blood flow distribution. When low-output syndrome is present for more than 1 hour, it usually reflects all three abnormalities.

1. Septic shock is the most common distributive abnormality, and volume repletion is an important initial consideration. Treatment of cardiogenic shock requires multiple autonomic interventions.
2. **Adverse Effects.** Side effects of α agonists most often reflect excessive α - or β -receptor activity.

D. Adrenergic Agonists

1. **Phenylephrine** is considered a pure α agonist that produces greater venoconstriction than arterial constriction. As a result, venous return and blood pressure are increased.
 - a. **Side Effects.** Excessive vasoconstriction produced by phenylephrine can elicit baroreceptor-mediated bradycardia with associated decreases in cardiac output. Increased systemic vascular resistance may further contribute to decreases in cardiac output and increases in myocardial oxygen requirements.
 - b. **Clinical Uses.** Phenylephrine is administered as a single dose (50–100 μg intravenously [IV]) to treat anesthetic-induced decreases in blood pressure and hypotension during cardiopulmonary bypass and as a continuous infusion to maintain perfusion pressure during cerebral and peripheral vascular procedures. Use of phenylephrine to maintain perfusion pressures during cerebral and peripheral vascular procedures must be done cautiously because it may evoke myocardial ischemia in susceptible patients.
2. **Norepinephrine** and methoxamine produce similar dose-related hemodynamic effects characterized by greater α than β effects.
 - a. Vasoconstriction increases systemic blood pressure but may also decrease tissue blood flow (especially renal blood flow) and increase myocardial oxygen requirements.

TABLE 15-3
DOSES AND PRINCIPAL SITES OF ACTION OF ADRENERGIC AGONISTS

Agent	Bolus (IV)	Continuous Infusion	α_1	α_2	β_1	β_2	Dopamine ₁	Dopamine ₂
Phenylephrine	50–100 μg	0.15 $\mu\text{g}/\text{kg}/\text{min}$ (10 mg in 250 mL, 40 $\mu\text{g}/\text{mL}$)	+++++	?	+/-	0	0	
Norepinephrine		0.1 $\mu\text{g}/\text{kg}/\text{min}$ (4 mL in 250 mL, 16 $\mu\text{g}/\text{mL}$)	+++++	+++++	+++	0	0	
Epinephrine	2–8 μg [*] 0.3– 0.5 μg [†]	0.015 $\mu\text{g}/\text{kg}/\text{min}$ (1 mL in 250 mL, 4 $\mu\text{g}/\text{mL}$)	+++++	+++++	+++++	++	0	
Ephedrine	5–10 mg		++ + to +++++	?	+++ +++++	++ ++	0 +++	?
Dobutamine		2–10 $\mu\text{g}/\text{kg}/\text{min}$ (200 mg in 250 mL, 800 $\mu\text{g}/\text{mL}$) 2–30 $\mu\text{g}/\text{kg}/\text{min}$ (250 mg in 250 mL, 1000 $\mu\text{g}/\text{mL}$)	0 to +	?	+++++	++	0	
Isoproterenol	4 μg	0.015 $\mu\text{g}/\text{kg}/\text{min}$ (0.15 $\mu\text{g}/\text{kg}/\text{min}$ to desired effect for third-degree heart block) 1 mg in 250 mL, 4 $\mu\text{g}/\text{mL}$	0	0	+++++	+++++	+++++	0

^{*}Dose to treat hypotension.

[†]Dose to treat cardiac arrest.

TABLE 15-4
HEMODYNAMIC EFFECTS OF ADRENERGIC AGONISTS

Drug	Heart Rate	Cardiac Output	Systemic Vascular Resistance	Venous Return	Renal Blood Flow
Phenylephrine	Decreased	Decreased	Increased	Increased	Decreased
Norepinephrine	Decreased	Decreased	Increased	Increased	Decreased
Epinephrine	Increased	Increased	Increased	Increased	Decreased
Ephedrine	Increased	Increased	Increased	Increased	Unpredictable
Dopamine	No change	Increased	Decreased to no change	Increased	Increased
Dobutamine	Increased	Increased	Decreased to no change	Unpredictable	Increased to no change
Isoproterenol	Increased	Increased	Decreased	Decreased	Increased to no change

- b. Continuous infusion of norepinephrine (which must be through a centrally placed IV catheter) to maintain systolic blood pressure above 90 mm Hg requires invasive monitoring and attention to fluid management.
 - c. In clinical conditions characterized by a low perfusion pressure and high flow (vasodilation) and maldistribution of flow, norepinephrine has been shown to improve renal and splanchnic blood flow by increasing perfusion pressure provided the patient has been volume resuscitated.
 3. **Epinephrine.** Whereas the α effects of epinephrine predominate in renal and cutaneous vasculature to decrease blood flow, the β effects increase blood flow to skeletal muscles.
 - a. **Side Effects.** Cardiac dysrhythmias are a hazard of excess β stimulation.
 - b. **Clinical Uses.** Epinephrine is administered to treat asthma (0.3–0.5 mg subcutaneously), treat cardiac arrest or life-threatening allergic reactions (0.3–0.5 mg IV), produce hemostasis (1:200,000 or 5 $\mu\text{g}/\text{mL}$ injected subcutaneously or submucosally), prolong regional anesthesia (0.2 mg added to local anesthetic solutions for spinal block or as a 1:200,000 concentration for epidural block), or provide a bloodless arthroscopic field by large-volume infusions of dilute epinephrine-containing solutions (1:200,000). (Unpredictable absorption of epinephrine, especially in denuded cancellous bone, may result in overdose and acute heart failure, pulmonary edema, cardiac dysrhythmias, and cardiac arrest in otherwise healthy patients.)
 4. **Ephedrine** produces cardiovascular effects that resemble those produced by epinephrine; however, its potency is greatly decreased, although its duration of action is about 10 times longer than that of epinephrine. Venoconstriction is greater than arterial constriction; thus, venous return and cardiac output are improved. A β effect increases heart rate and further facilitates cardiac output. The α and β effects of ephedrine result in a modest and predictable increase in blood pressure.

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- a. **Side Effects.** Tachycardia and cardiac dysrhythmias are possible but less likely to occur than after administration of epinephrine.
 - b. **Clinical Uses.** Ephedrine is the most commonly used vasopressor (5–10 mg IV) to treat decreases in blood pressure produced by anesthesia (especially regional blocks) and is considered the drug of choice in obstetrics because uterine blood flow directly parallels ephedrine-induced increases in blood pressure. It is appropriate to administer ephedrine as a temporizing measure to restore perfusion pressure while the underlying cause of hypotension is corrected.
5. **Isoproterenol** is a nonspecific β -agonist that lacks α -agonist effects. Whereas cardiac output is increased by virtue of increases in heart rate as well as increased myocardial contractility, decreases in systemic vascular resistance contribute to decreased afterload.
- a. **Side Effects.** Myocardial ischemia may be evoked in vulnerable patients (increased myocardial oxygen requirements caused by tachycardia and increased myocardial contractility paralleled by decreased coronary oxygen delivery because of decreased diastolic blood pressure). Increases in cardiac output may be diverted to nonvital tissues such as skeletal muscles.
 - b. **Clinical Uses.** Isoproterenol is most often administered as a continuous IV infusion for the treatment of congestive heart failure associated with bradycardia, asthma, or pulmonary hypertension. This catecholamine acts as a chemical cardiac pacemaker in the presence of complete heart block.
6. **Dobutamine** is a synthetic catecholamine derived from isoproterenol that acts directly on β_1 receptors and does not cause norepinephrine release or stimulation of dopamine receptors. Weak α_1 -agonist effects of dobutamine may be unmasked by β -blockade. Dobutamine produces a positive inotropic effect with minimal effects on heart rate and systemic vascular resistance (an advantage over isoproterenol).
- a. **Side Effects.** Increases in automaticity of the SA node and increases in conduction of cardiac impulses through the AV node and ventricles

may occur, emphasizing the need for caution in administering this drug to patients with atrial fibrillation or other tachydysrhythmias.

Dobutamine may increase heart rate more than epinephrine for a given increase in cardiac output.

- b. **Clinical Uses.** Dobutamine is most often administered (2–30 $\mu\text{g}/\text{kg}/\text{min}$ IV) for its inotropic effects in patients with poor myocardial contractility, such as after cardiopulmonary bypass.
7. **Dopamine** is an agonist at dopaminergic (0.5–2.0 $\mu\text{g}/\text{kg}/\text{min}$ IV), β (2 to 10 $\mu\text{g}/\text{kg}/\text{min}$ IV), and α (>10 $\mu\text{g}/\text{kg}/\text{min}$ IV) receptors. Infusion rates above 10 $\mu\text{g}/\text{kg}/\text{min}$ IV may produce sufficient vasoconstriction to offset desirable dopaminergic (increases renal blood flow) and β (increased cardiac output) receptor stimulation. The concept of “renal dose” dopamine (0.5–2.0 $\mu\text{g}/\text{kg}/\text{min}$ IV) is considered outdated. Despite the apparent dose–response dependency of dopamine, a wide variability of individual responses has been observed.
 - a. **Side Effects.** Tachycardia and cardiac dysrhythmias occur infrequently. Extravasation of dopamine can produce gangrene. Pulmonary artery pressure may be increased, detracting from the use of dopamine in patients with right-sided heart failure. Insulin secretion is inhibited, explaining the common occurrence of hyperglycemia during infusion of dopamine.
 - b. **Clinical Uses.** Dopamine is most often administered as a continuous IV infusion (2–10 $\mu\text{g}/\text{kg}/\text{min}$) for its inotropic and diuretic effects in patients with poor myocardial contractility, such as after cardiopulmonary bypass.
 8. **Combination therapy** is most often with dopamine and dobutamine in an attempt to maximize positive inotropic effect with less vasoconstriction.
 - E. **Fenoldopam** is a selective dopamine₁ agonist with no α or β activity compared with dopamine.
 - F. **Clonidine** is a centrally acting selective partial α_2 agonist. It is an antihypertensive drug by virtue of its ability to decrease central sympathetic outflow.
 1. **Side Effects.** Sedation, bradycardia, and dry mouth from sympatholytics are common. Abrupt

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discontinuation of clonidine, as before surgery, may result in rebound hypertension, especially if the daily dose is above 1.2 mg. This hypertension may be confused with a response to emergence from anesthesia, but it is typically delayed for about 18 hours. Transdermal administration of clonidine is an alternative to the oral route because an IV preparation is not available. Life-threatening hypertension after withdrawal may be treated with nitroprusside.

2. **Clinical Uses.** In addition to its antihypertensive effect, clonidine administered preoperatively (5 $\mu\text{g}/\text{kg}$ orally) attenuates SNS reflex responses, such as those associated with direct laryngoscopy or surgical stimulation, and greatly decreases anesthetic requirements ($\geq 40\%$) for volatile drugs or opioids. When placed in the subarachnoid or epidural space, this drug produces analgesia that may be accompanied by sedation and bradycardia but not depression of ventilation.

G. Dexmedetomidine is a more selective α_2 agonist than clonidine. A stereoselective ability to interact with receptors resulting in decreased anesthetic requirements is evidence for an “anesthetic receptor.”

1. This drug produces excellent sedation (no depression of ventilation but upper airway obstruction may occur), produces analgesia, reduces blood pressure and heart rate (promotes hemodynamic stability), and greatly decreases plasma catecholamines.
2. The loading infusion of 1 $\mu\text{g}/\text{kg}$ is administered over 10 minutes in a monitored setting.

VI. NONADRENERGIC SYMPATHOMIMETIC AGENTS

A. Vasopressin (and its congener, desmopressin) are exogenous preparations of the endogenous antidiuretic hormone.

1. Clinical uses of vasopressin have included treatment of diabetes and as an adjunct to treatment of gastrointestinal (GI) bleeding and esophageal varices.
2. New clinical indications for vasopressin include support of patients with septic shock and cardiac

arrest (40 IU in 40 mL IV) secondary to ventricular fibrillation or pulseless ventricular tachycardia. Advanced Cardiac Life Support (ACLS) guidelines recommend vasopressin in place of the first or second dose of epinephrine during treatment of pulseless arrest.

- B. Adenosine** is an endogenous byproduct of ATP and has negative chronotropic effects on the SA node as well as negative dromotropic effects on the AV node when administered IV. The principal clinical use of adenosine is termination of paroxysmal supraventricular tachycardia (6 mg IV [100–150 μ g/kg IV for pediatric patients]).
- C. Phosphodiesterase inhibitors** do not rely on stimulation of α or β receptors. These drugs combine positive inotropism with vasodilator activity by selectively inhibiting phosphodiesterase.
- 1. Milrinone** is a more potent phosphodiesterase inhibitor that lacks effects on platelets and may be useful for short-term IV therapy of congestive heart failure.
- D. Digitalis Glycosides.** Digoxin is administered principally to treat congestive heart failure and control supraventricular tachydyrhythmias such as atrial fibrillation. A therapeutic effect occurs within 10 minutes (0.25–1.0 mg IV for adults). Signs of digitalis toxicity (cardiac dysrhythmias, GI disturbances) must be inquired about when evaluating patients preoperatively. Digitalis toxicity is enhanced by hypokalemia or injection of calcium. Iatrogenic hyperventilation of the lungs with associated hypokalemia should be avoided during anesthesia. Most recommend continuation of digitalis therapy in the perioperative period, especially when the drug is being administered for heart rate control. Prophylactic preoperative administration of digitalis preparation is controversial but may be of unique value in elderly patients undergoing thoracic surgery.

VII. SYMPATHOLYTIC DRUGS

- A. α Antagonists** produce orthostatic hypotension, tachycardia, and miosis.
- 1. Phentolamine** is a nonselective and competitive antagonist at α_1 and α_2 receptors that is typically

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administered (2–5 mg IV) until adequate control of blood pressure is achieved. Tachycardia reflects continued presynaptic release of norepinephrine owing to α_2 -receptor blockade.

2. **Prazosin** is a selective postsynaptic α_1 antagonist that leaves intact the negative feedback mechanism for norepinephrine release that is mediated by presynaptic α_2 activity. This drug is useful in the preoperative preparation of patients with pheochromocytoma.
- B. β Antagonists** are distinguished by differing pharmacokinetic and pharmacodynamic characteristics (Table 15-5).
1. An important class of drugs is beta-blockers, which are indicated for the treatment of coronary artery disease, hypertension, heart failure, and tachyarrhythmias. They have a primary role in treatment of patients after myocardial infarction (MI). Beta-blockers decrease mortality in patients with heart failure caused by left ventricular systolic dysfunction. They also reduce the incidence of perioperative MI and may be useful perioperatively in high-risk patients undergoing vascular and other high-risk surgical procedures.
 2. Selective beta blockade (**cardioselective**) implies greater safety in the treatment of patients with obstructive pulmonary disease, diabetes mellitus, and peripheral vascular disease because β_2 -agonist effects (bronchodilation, vasodilation) are presumably maintained. The clinical significance of membrane-stabilizing activity (a local anesthetic effect on myocardial cells at high doses) and intrinsic sympathomimetic activity (partial β -agonist activity at low doses) has not been documented. Because of their selectivity, the use of beta-blockers has extended to include treatment of congestive heart failure.
 3. **Propranolol** is a nonselective β antagonist that may be administered in single IV doses of 0.1 to 0.5 mg (maximum dose, \sim 2 mg) to slow heart rate during anesthesia. Additive negative inotropic or chronotropic effects with inhaled or injected anesthetics are likely to occur but have not been a significant clinical problem.
 4. **Timolol** is administered as a topical preparation for the treatment of glaucoma. There may be sufficient

TABLE 15-5
PHARMACOKINETICS OF β ANTAGONISTS

Drug	Relative β_1 Selectivity	Membrane Stabilizing Activity	Intrinsic Sympathomimetic Activity	Elimination Half-Time (hr)	Lipid Solubility	Route of Elimination
Propranolol	0	+	0	3-4	+++	Hepatic
Metoprolol	++	0	0	3-4	+	Hepatic
Atenolol	++	0	0	6-9	0	Renal
Esmolol	++	0	0	0.16	?	Plasma esterase
Timolol	0	0	0	4-5	+	Hepatic Renal

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systemic absorption to cause bradycardia and hypotension that are resistant to reversal with atropine.

5. Mixed Antagonists

- a. **Labetalol** produces selective α_1 - and nonselective β -antagonist effects. Administered as a single dose (0.05–0.15 mg/kg IV over 2 minutes), this drug is useful in controlling hypertension and tachycardia in response to painful stimulation during general anesthesia. Although the magnitude is less than with β antagonists, worsening of congestive heart failure or appearance of bronchospasm may occur after administration of labetalol.

VIII. CALCIUM CHANNEL BLOCKERS

Interact with cell membranes to interfere with movement of calcium into cells through ion-specific channels (known as slow channels because their transition among the resting, activated, and inactivated states is delayed compared with fast sodium channels). Calcium channel blockers are a heterogeneous group of drugs with dissimilar structures and different electrophysiologic and pharmacologic properties. These drugs are most useful for the treatment of supraventricular tachydyrhythmias and coronary artery vasospasm (Table 15-6).

TABLE 15-6
COMPARATIVE EFFECTS OF CALCIUM CHANNEL BLOCKERS

	Verapamil	Nifedipine	Diltiazem
Dose			
IV (μ g/kg)	75–150	5–15	75–150
PO (mg every 8 hr)	80–160	10–20	60–90
Negative inotropy	+	0	0/+
Negative chronotropy	+	0	0/+
Negative dromotropy	++++	0	+++
Coronary artery vasodilation	++	++++	+++
Systemic vasodilation	++	++++	++
Bronchodilation	0/+	0/+	
Elimination half-time (hr)	2–7	4–5	4
Route of elimination	Renal	Renal	Hepatic

IV = intravenous; PO = per os.

- A. Verapamil** is the drug of choice for termination of supraventricular dysrhythmias, and it is also effective in slowing the heart rate in patients with atrial fibrillation and atrial flutter. There is a dose-dependent increase in the P-R interval on the electrocardiogram and a delay in conduction of cardiac impulses through the AV node.
1. Caution must be exercised when treating patients with Wolff-Parkinson-White syndrome because verapamil may increase conduction velocity in the accessory tract.
 2. Unlike β antagonists, verapamil does not increase airway resistance in patients with obstructive pulmonary disease.
- B. Nifedipine** is more effective than nitroglycerin for treatment of angina pectoris caused by coronary artery vasospasm.
1. Vasodilation results in compensatory tachycardia, and cardiac output may increase as a result of after-load reduction.
 2. Administration of nifedipine is useful during anesthesia when there is evidence of myocardial ischemia associated with hypertension.
- C. Diltiazem** is an effective coronary artery vasodilator but a poor peripheral vasodilator; it may produce bradycardia.
- D. Nicardipine** produces vasodilation of coronary arterioles without altering activity of the sinus node or conduction of cardiac impulses through the AV node.
- E. Nimodipine** is a highly lipophilic drug that produces somewhat selective vasodilation of cerebral arteries, resulting in a favorable effect on the severity of neurologic deficits caused by cerebral vasospasm after subarachnoid hemorrhage.
- F. Calcium Channel Blockers and Anesthesia.** These drugs may exhibit additive myocardial depressant effects with volatile anesthetics, which may also interfere with inward calcium movement. Opioids do not seem to alter the response to calcium channel blockers. Calcium channel blockers seem to augment the effects of both depolarizing and nondepolarizing muscle relaxants in a manner similar to those of “mycin” antibiotics.

IX. ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

- A. Inhibitors of angiotensin-converting enzyme (captopril, enalapril, lisinopril) prevent the conversion of angiotensin I to angiotensin II. These drugs are effective in the treatment of congestive heart failure and essential hypertension as well as renovascular and malignant hypertension.
- B. Side effects are minor, with the principal cardiovascular effect being decreasing systemic vascular resistance.

X. VASODILATORS

Vasodilators decrease blood pressure by dose-related direct effects on vascular smooth muscle independent of α or β receptors (Table 15-7). These drugs may evoke baroreceptor-mediated increases in heart rate.

Combination with a β -antagonist may be necessary to offset this reflex tachycardia (maintain heart rate <100 bpm).

- A. **Hydralazine** (5–10 mg IV every 10 to 20 minutes) is useful to control perioperative hypertension.

TABLE 15-7
DOSES AND SITES OF ACTION OF VASODILATORS

Drug	Bolus (Adult, IV)	Continuous Infusion (Adult, IV)	Site of Action	Onset	Duration
Hydralazine	5–10 mg		Arterial	15–20 min	4–6 hr
Nitroprusside	50–100 μ g	0.25–5 μ g/kg/min (50 mg in 250 mL, 200 μ g/mL)	Arterial Venous	1–2 min	2–5 min
Nitroglycerin		0.25–3 μ g/kg/min (50 mg in 250 mL, 200 μ g/mL)	Venous Arterial	2–5 min	3–5 min

- B. Nitroprusside** is administered as a continuous infusion (0.25–0.5 $\mu\text{g}/\text{kg}/\text{min}$ IV) using an infusion pump and continuous monitoring of blood pressure. The dose is increased slowly as needed to control hypertension or to produce controlled hypotension. Rarely is more than 3 to 5 $\mu\text{g}/\text{kg}/\text{min}$ of nitroprusside required in an anesthetized patient. Acute hypertensive responses can be treated with single IV doses of 50 to 100 μg .
1. The hypotensive effect of nitroprusside reflects direct relaxation of arterial and venous smooth muscle, causing decreases in preload and afterload. Hypotensive effects of nitroprusside are potentiated by volatile anesthetics and blood loss.
 2. **Side Effects.** The ferrous iron of nitroprusside reacts with sulfhydryl groups in red blood cells and releases cyanide, which is reduced to thiocyanate in the liver. High doses of nitroprusside (>10 $\mu\text{g}/\text{kg}/\text{min}$ IV) may result in cyanide toxicity. There is no evidence that renal or hepatic diseases increase the likelihood of cyanide toxicity.
 - a. **Diagnosis.** Tachyphylaxis, increased venous oxygen tension, and metabolic acidosis signal the development of cyanide toxicity (cyanide binds to cytochrome oxidase, causing cellular hypoxia) and the need to discontinue the infusion of nitroprusside immediately.
 - b. **Treatment** of cyanide toxicity is with sodium thiosulfate (150 mg/kg IV in 50 mL of water) administered over 15 minutes to speed the conversion of cyanide to thiocyanate.
- C. Nitroglycerin** is administered as a continuous infusion (0.25–3.0 $\mu\text{g}/\text{kg}/\text{min}$ IV) to treat myocardial ischemia. Its predominant action is on venules, causing increased venous capacitance and decreased venous return.
1. Control of hypertension with nitroglycerin is less reliable than with nitroprusside, emphasizing the minimal effect of this drug on arterial smooth muscle.
 2. Unlike nitroprusside, nitroglycerin poses no risk of cyanide toxicity. For this reason, nitroglycerin may be chosen over nitroprusside to control hypertension associated with pregnancy-induced hypertension.
- D. Nesiritide** is a recombinant form of human B-type natriuretic peptide that produces beneficial hemodynamic effects by venous and arterial vasodilation, including coronary vasodilation.