13
Cardiovascular Pharmacology

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KEY POINTS

1 Drugs that mimic the effects of acetylcholine are most commonly used in ophthalmology.

2 Anticholinesterases prolong the actions of acetylcholine by preventing its metabolism; these drugs are used clinically for reversal of neuromuscular blockade and treatment of central anticholinergic syndrome.

3 Muscarinic antagonists inhibit the effects of acetylcholine mediated through the parasympathetic nervous system.

4 The cardiovascular effects of endogenous and synthetic catecholamines are dependent on their specificity for α- and β-adrenoceptor subtypes.

5 Catecholamines have well-documented utility in the treatment of acute left ventricular dysfunction, but may cause arrhythmias, hypertension, and myocardial ischemia.

6 α_1-Adrenoceptor antagonists not only reduce arterial pressure but also produce reflex tachycardia and orthostatic hypotension, especially in patients with hypovolemia.

7 The α_2-adrenoceptor agonists clonidine and dexmedetomidine are used extensively for sedation, anxiolysis, and analgesia.

8 β-Blockers play major roles in the treatment of hypertension, coronary artery disease, myocardial infarction, and heart failure.

9 Milrinone and levosimendan are important medications for the management of acute left ventricular dysfunction and cause synergistic positive inotropic effects when administered with catecholamines by enhancing intracellular cAMP-mediated signaling.

10 Vasopressin is the most potent arterial vasoconstrictor currently available and is useful for treatment of vasoplegia associated with sepsis or cardiac surgery.

11 Calcium channel blockers reduce arterial pressure and dilate coronary arteries, but some of these drugs also affect sinoatrial node automaticity and atrioventricular node conduction. These latter actions may be beneficial in the presence of supraventricular tachyarrhythmias.

12 Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are useful for the treatment of hypertension and heart failure.

Introduction

This chapter discusses the pharmacology of medications that affect the autonomic nervous and cardiovascular systems. A thorough understanding of the pharmacology of cholinergic and anticholinergic drugs, endogenous and synthetic catecholamines, sympathomimetics, α_1-antagonists, α_2-agonists, β-blockers, phosphodiesterase inhibitors, digitalis glycosides, vasopressin, and antihypertensive medications including nitrovasodilators, calcium (Ca^{2+}) channel blockers, and angiotensin-converting enzyme (ACE) inhibitors is essential for the practice of anesthesiology. Each of these drug classifications will be reviewed in detail, with primary emphasis on their cardiovascular actions.

Cholinergic Drugs

1 Cholinergic drugs mimic (e.g., agonists such as methacholine), enhance (e.g., anticholinesterase inhibitors including neostigmine), or block (e.g., antagonists such as atropine) the actions of acetylcholine (ACh) in autonomic ganglia and skeletal muscle at nicotinic receptors or in parasympathetic postganglionic neurons through muscarinic receptors. In general, cholinergic drugs have greater site-specificity and exert more prolonged effects than the primary neurotransmitter. Compared with the plethora of medications that affect the sympathetic nervous system (see below), there are relatively few drugs in current clinical use that influence the function of parasympathetic nervous system by modulating ACh's actions or metabolism. ACh itself has virtually no therapeutic applications because of its diffuse action, extensive side effect profile, and rapid hydrolysis by acetylcholinesterase and butyrylcholinesterase (pseudocholinesterase). Topical ACh eye drops are occasionally used when acute miosis is required during ophthalmologic surgery (e.g., cataract extraction) or for the treatment of glaucoma. Under these circumstances, systemic cholinergic effects are usually not observed because little ACh uptake occurs and ACh is quickly metabolized.

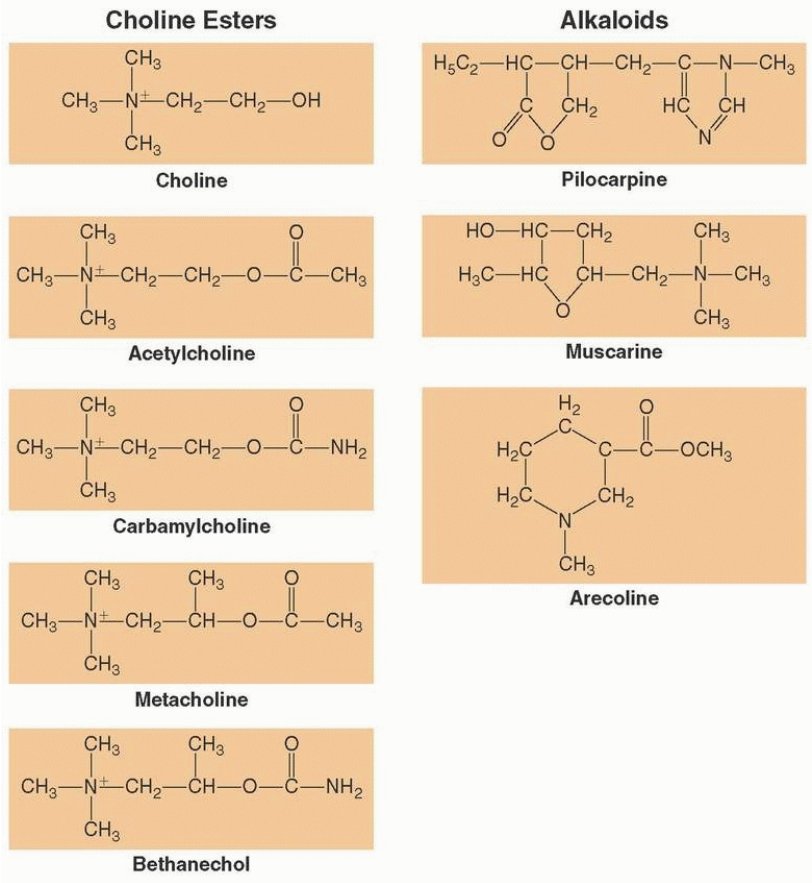


Figure 13-1 Chemical structures of direct acting cholinergic-mimetic esters and alkaloids.

Cholinergic Agonists

Synthetic cholinergic agonists are not used in anesthesia practice, but understanding of their pharmacology remains important because anesthesiologists often encounter patients who are treated with them (Fig. 13-1; Table 13-1). ACh is a quaternary ammonium compound that causes changes in membrane conformation when it interacts with postsynaptic receptors, increasing the permeability to Na^+, K^+, and Cl^- ions down their respective electrochemical gradients and causing membrane depolarization. Structure-activity relationships identified two important binding sites on the postsynaptic ACh receptor that are crucial for this process: the "ester" site that binds this moiety of the molecule and an "ion" site through which the quaternary amine is bound. Subtle differences in the chemical structure of cholinergic drugs

are capable of producing more muscarinic and less nicotinic specificity while simultaneously reducing the rate of the drug's metabolism. Two major classes of cholinergic agonists have been developed based on modification of these structural components: choline esters and alkaloids. For example, β-methylation of the choline moiety produces methacholine, a synthetic cholinergic drug that is a muscarinic agonist and is almost entirely resistant to cholinesterase hydrolysis. Methacholine is used almost exclusively as a provocative agent for identifying the presence of reactive airway disease in subjects who do not have clinically apparent signs or symptoms of asthma. Methacholine causes bronchoconstriction, increases airway secretions, and reduces peak expiratory flow rate via activation of bronchial muscarinic M_3 receptors.[1] Not surprisingly, methacholine may also produce bradycardia and hypotension as a result of M_3 receptor activation in myocardium and vascular endothelium, respectively. Methacholine-induced stimulation of M_3 receptors activates the pertussis toxin-insensitive $G_{q/11}$ protein coupled-phospholipase C-inositol triphosphate (IP_3)-mediated signaling cascade, culminating in endothelial nitric oxide synthase activation, nitric oxide production, and dilation of vascular smooth muscle.[2] Use of methacholine is relatively contraindicated in patients with known asthma or chronic obstructive pulmonary disease, essential hypertension, recent cerebrovascular accident, or myocardial infarction because marked bronchospasm or profound hypotension may occur. Indeed, emergency airway equipment, oxygen, inhaled β_2-adrenoceptor agonists, and resuscitative medications should be readily available during methacholine provocative testing.

Table 13-1 Comparative Muscarinic Actions of Direct Cholinomimetic Agents

	Systemic				
	Acetylcholine	*Methacholine*	*Carbamylcholine*	*Bethanechol*	*Pilocarpine*
Esterase Hydrolysis	+++	+	0	0	0
Eye (Topical)					
Iris	++	++	+++	+++	+++
Ciliary	++	++	+++	+++	++
Heart					

Rate	-	-	-	-	
Contractility	-	-	-	-	
Conduction	-	-	-	-	
Smooth Muscle					
Vascular	-	-	-	-	--
Bronchial	++	++	+	+	++
Gastrointestinal motility	++	++	+++	+++	++
Gastrointestinal sphincters	-	-	-	-	++
Biliary	++	++	+++	+++	++
Bladder					
Detrusor	++	++	+++	+++	++
Sphincter	-	-	-	-	-
Exocrine Glands					
Respiratory	+++	++	+++	++	++++
Salivary	++	++	++	++	+++++
Pharyngeal	++	++	++	++	++++
Lacrimal	++	++	++	++	++++
Sweat	++	++	++	++	+++++
Gastrointestinal acid and secretions	++	++	++	++	++++
Nicotinic Actions	+++	+	+++	-	+++

+, stimulation; -, inhibition.

Bethanechol is a choline ester (a carbamate derivative of methacholine) that is relatively selective for the M_3 receptors in the urinary and gastrointestinal tracts with relative sparing of the cardiovascular and respiratory systems. Bethanechol is useful for treatment of nonobstructive urinary retention during the postoperative period or in some cases of neurogenic bladder as an alternative to chronic catheterization.[3] Bethanechol also increases gastrointestinal motility and stimulates peristalsis. The drug was previously used for treatment of postoperative abdominal distention, gastric atony, and gastroesophageal reflux disease, but more efficacious medications are now available for these conditions. Carbamylcholine is another choline ester derivative that is used topically to produce miosis in patients with wide-angle glaucoma. Pilocarpine is an alkaloid cholinergic agonist used as a topical miotic agent to reduce intraocular pressure in patients with glaucoma. Oral pilocarpine may also be used to increase salivary and lacrimal gland production in patients with xerostomia after head and neck irradiation or in those with Sjögren syndrome.[4] Finally, muscarinic agonists may also be useful for treatment of cognitive impairment in patients with Alzheimer disease.

Cholinesterase Inhibitors

2 Cholinesterase inhibitors (anticholinesterases) are essential to anesthesiologists because these medications are used to produce the sustained cholinergic effect necessary to overcome nondepolarizing neuromuscular blockade. These drugs are also used for treatment of myasthenia gravis, glaucoma, and, less commonly, intestinal or urinary bladder atony and have important anesthetic implications. The pharmacology of anticholinesterases as neuromuscular blockade reversal medications is described in detail in Chapter 21; the current discussion will focus solely on the actions of these drugs as cholinergic-mimetics. In contrast to organophosphate compounds (e.g., pesticides such as malathion and parathion; nerve toxins including sarin, soman, and VX) that irreversibly inhibit acetylcholinesterase and butyrylcholinesterase, clinically used cholinesterase inhibitors (e.g., neostigmine, edrophonium) reversibly inhibit these enzymes, which very rapidly hydrolyze ACh (half-life of microseconds) into acetate and choline molecules under normal conditions, thereby inactivating the neurotransmitter. This inhibition of acetylcholinesterase and butyrylcholinesterase allows the actions of ACh at postganglionic muscarinic receptors to be markedly amplified, resulting in intense parasympathetic nervous system activity similar to that produced by direct cholinergic agonists. The unimpeded accumulation of ACh also causes dual actions on autonomic nervous system ganglia and skeletal muscle, initially stimulating but subsequently depressing neurotransmission through their nicotinic receptors. Similar initial stimulation followed by depression of central nervous system cholinergic receptors also occurs with exposure to a lethal dose of an anticholinesterase, for example, when an organophosphate overdose occurs during its use as a pesticide or when the agent is used as a chemical weapon during warfare or a terrorist attack.[5]

Clinically used cholinesterase inhibitors are either carbamoyl esters (including neostigmine, physostigmine, and pyridostigmine) or quaternary ammonium alcohols (edrophonium; Fig. 13-2). Three areas on the acetylcholinesterase molecule are capable of binding inhibitory ligands: two are located in the active center of the enzyme (the acyl pocket and a choline subsite, referred to collectively as the “esteratic” site), whereas the third is a peripheral “anionic” site.[6] The specificity and duration of action of

cholinesterase inhibitors depend on their binding site, affinity, and rate of hydrolysis. For example, edrophonium reversibly binds to the choline subsite, but the cholinesterase inhibitor's chemical structure facilitates its rapid renal excretion and contributes to the drug's relatively short duration of action (approximately 1 hour). The carbamate cholinesterase inhibitors also bind to acetylcholinesterase's "esteratic" site, but these drugs are more slowly metabolized because their carbamoyl ester linkage is less susceptible to hydrolysis, thereby extending their clinical duration of action to approximately 4 hours. In contrast, organophosphates bind irreversibly to the active center of anticholinesterase and require stimulated hydrolysis of the phosphate-enzyme complex to restore the enzyme's activity with drugs such as pralidoxime (2-PAM). Organophosphates are particular insidious toxins because they may be odorless, are rapidly absorbed through the skin, are very lipid-soluble, and move freely into the central nervous system.[7]

The most prominent pharmacologic effects of the cholinesterase inhibitors are their actions on muscarinic receptors, but when used to reverse nondepolarizing neuromuscular blockade, the intended target of these drugs is the nicotinic receptors at the motor endplate of skeletal muscle. Notably, higher concentrations of ACh are required to activate nicotinic than muscarinic receptors. Thus, the relative excess of ACh needed to overcome nondepolarizing neuromuscular blockade of nicotinic receptors predictably causes profound stimulation of muscarinic receptors and cholinergic side effects. As a result, administration of a muscarinic antagonist (e.g., atropine, glycopyrrolate) is most often required to block the side effects of cholinesterase inhibitors (e.g., bradycardia, hypotension, bronchospasm, sialorrhea, miosis, increased intestinal motility, sphincter relaxation) while sparing the actions of these drugs at the nicotinic receptors. Unlike neostigmine, pyridostigmine, and edrophonium, physostigmine is a tertiary amine that readily crosses the blood-brain barrier and inhibits acetylcholinesterase in the central nervous system. As a result, physostigmine is effective for the treatment of atropine or scopolamine overdose (these muscarinic antagonists also penetrate the blood-brain barrier) and central anticholinergic syndrome (see below).[8]

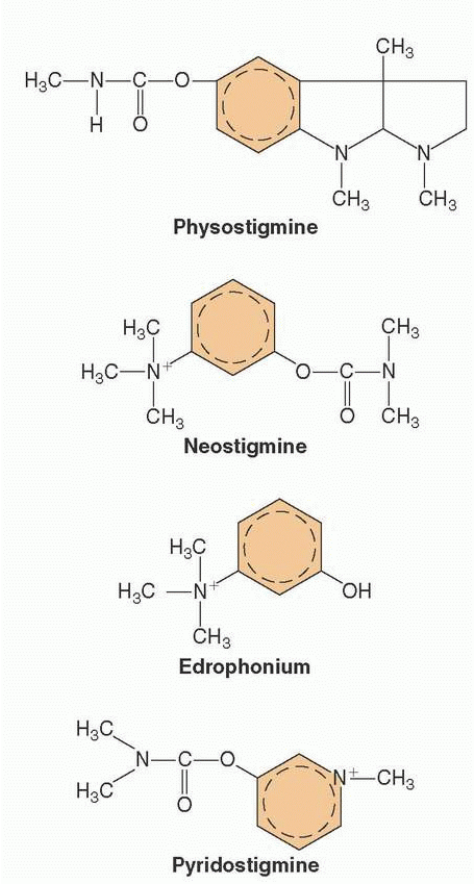


Figure 13-2 Chemical structures of clinical anticholinesterases.

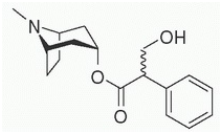
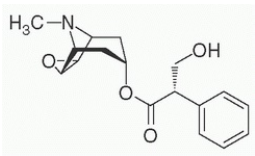
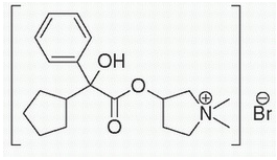
Echothiophate iodide is the only clinically used organophosphate cholinesterase inhibitor, which is applied topically for the treatment of glaucoma because of its miotic effect. The drug's primary advantage over other topical glaucoma medications is its prolonged duration of action. Indeed, echothiophate may remain clinically effective for several weeks after cessation of therapy. Topical absorption of echothiophate is highly variable but can be considerable. As a result, succinylcholine may have a prolonged duration of action in patients treated with echothiophate. Despite this theoretical concern, the use of succinylcholine should not be expressly avoided when the depolarizing neuromuscular blocker is clinically indicated.

Muscarinic Antagonists

3 The muscarinic antagonists atropine, scopolamine, and glycopyrrolate are commonly used in anesthesia practice (Table 13-2).

Atropine and scopolamine are belladonna alkaloids that are derived from a variety of plant species (including deadly nightshade shrub, jimson weed, and henbane) and have been used for millennia as toxins and therapeutic agents. Muscarinic antagonists are competitive inhibitors of ACh at parasympathetic muscarinic receptors and act to increase heart rate; inhibit salivary, bronchial, and gastrointestinal secretions; attenuate gastric acid production; reduce gastrointestinal motility; cause bronchodilation; and antagonize the muscarinic side effects of anticholinesterases during reversal of neuromuscular blockade. Notably, the drugs also bind to presynaptic muscarinic receptors on norepinephrine-secreting postganglionic neurons. This action may enhance sympathetic nervous system activity because Achinduced stimulation of these presynaptic receptors normally inhibits norepinephrine release, whereas muscarinic blockade abolishes this inhibition.[9] Anesthesiologists first used atropine to mitigate excessive salivation and attenuate vagal-mediated bradycardia during open-drop ether or chloroform anesthesia. These antiquated indications are no longer of relevance in modern practice, but anesthesiologists continue to exploit the antisialagogue effect of muscarinic antagonists (particularly glycopyrrolate) in preparation for fiberoptic intubation or during some otolaryngology or dental procedures in adults and children. Although the potencies of atropine, scopolamine, and glycopyrrolate are quite different, the drugs have little or no muscarinic receptor subtype specificity, and as a result, exert similar anticholinergic effects in most target organs except for the heart and central nervous system. In contrast, selective muscarinic subtype receptor antagonists have also been synthesized and are now used extensively for treatment of overactive bladder conditions[10] without causing pronounced adverse systemic anticholinergic effects.

Table 13-2 Comparative Effects of Muscarinic Antagonists

Name	Chemical Structure	Duration IV (hrs)	Duration IM (hrs)	CNS	Heart Rate	Antisialagogue Effect	Mydriasis Cycloplegia
Atropine		0.25-0.5	2-4	Stimulation	+++	+	+
Scopolamine		0.5-1	4-6	Sedation	0	++	+
Glycopyrrolate		2-4	6-8	0	+	++	0

Atropine and scopolamine are tertiary amines that easily penetrate the blood-brain barrier and produce central nervous system effects. For example, scopolamine is primarily a central nervous system depressant that causes sedation, amnesia, and euphoria. When combined with an intravenous long-acting opioid (e.g., morphine, meperidine), these properties made scopolamine particularly useful as intramuscular premedication for patients undergoing cardiac or major noncardiac surgery before midazolam was introduced into clinical practice in the 1980s. Transdermal scopolamine is currently used for prophylaxis against kinetosis (motion sickness) and is also effective for the treatment of postoperative nausea and vomiting, but the drug may be associated with anticholinergic side effects despite this route of administration. Lower doses of atropine are relatively devoid of central nervous system effects, but higher doses (≥2 mg; used most often in combination with an anticholinesterase inhibitor to reverse neuromuscular blockade or for the treatment of symptomatic bradyarrhythmias) often produce restlessness, disorientation, hallucinations, and delirium. In contrast to atropine and scopolamine, the synthetic muscarinic antagonist glycopyrrolate is a quaternary amine that does not cross the blood-brain barrier and is devoid of central nervous system effects. When combined with glycopyrrolate's more prolonged duration of action, this latter property makes the muscarinic antagonist more attractive for routine clinical use in anesthesiology than atropine.

Atropine, and to a lesser extent glycopyrrolate, increase heart rate when sinus bradycardia occurs as a result of vagal stimulation (e.g., peritoneal traction during abdominal surgery) or inhibition of cardiac sympathetic nerve traffic during spinal or epidural anesthesia. Atropine is also a treatment of choice for symptomatic bradyarrhythmias (e.g., second- or third-degree heart block). Conversely, atropine must be used with extreme caution when tachycardia is deleterious (e.g., coronary artery stenosis, aortic valve stenosis, hypertrophic obstructive cardiomyopathy, pheochromocytoma, thyroid storm). Paradoxically, very low doses of atropine (<0.1 mg) may decrease heart rate[11] through blockade of presynaptic parasympathetic neuron M_1 receptors.[12] Scopolamine most often produces little or no change in heart rate when administered through an intramuscular route for premedication. Notably, both clinically used belladonna alkaloids are capable of producing a paradoxical bradycardia when lower doses of these drugs are administered (scopolamine to a greater extent than atropine). Atropine and scopolamine cause mydriasis and cycloplegia because they exert muscarinic antagonist effects on Ach-mediated cranial nerve II (afferent) and III (efferent) control of pupillary reactivity and ocular accommodation. Indeed, atropine-mimetics are widely used in ophthalmology because

pupillary dilation facilitates visual inspection of the posterior chamber and retina. Not surprisingly, muscarinic antagonists are relatively contraindicated in patients with narrow-angle glaucoma because pupillary dilation thickens the peripheral iris and narrows the iridocorneal angle, thereby mechanically impairing aqueous humor drainage and increasing intraocular pressure. Muscarinic antagonists inhibit sympathetic nervous system innervation of sweat glands because ACh is the neurotransmitter in these postganglionic neurons. Pediatric patients are particularly susceptible to develop hyperthermia when treated with these drugs because children are more reliant on sweating to maintain normal body temperature than adults. Muscarinic antagonists may also be relatively contraindicated in febrile patients for similar reasons.

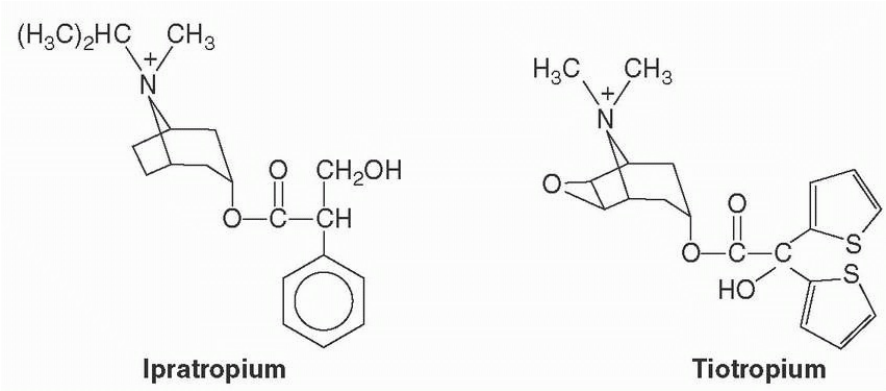


Figure 13-3 Chemical structures of inhaled muscarinic antagonists.

Ipratropium and tiotropium are muscarinic antagonists that resemble atropine and are used for the treatment of reactive airway disease (Fig. 13-3).[13,14] The drugs are bronchial smooth muscle dilators that are administered using metered-dose inhalers. Bronchodilation produced by ipratropium and tiotropium is less pronounced than that

observed with β_2-adrenoceptor agonists. Nevertheless, ipratropium and tiotropium effectively inhibit airway reactivity induced by a variety of provocative substances (methacholine, histamine, prostaglandin $F_{2-\alpha}$), but they are ineffective against leukotriene-induced bronchoconstriction. Neither drug substantially affects mucociliary clearance. Because of their quaternary ammonium structures, ipratropium and tiotropium are poorly absorbed into the systemic circulation and do not produce adverse anticholinergic side effects with the exception of xerostomia. The inhaled muscarinic antagonists may be more efficacious in patients with chronic obstructive pulmonary disease than in those suffering from asthma.[15]

Muscarinic Antagonist Toxicity

Atropine and other muscarinic antagonists cause symptoms associated with blockade of Ach at parasympathetic and sympathetic (sweat glands) postganglionic neurons (Table 13-3). The familiar medical school mnemonic "dry as a bone; red as a beet; blind as a bat; hot as a hare; mad as a hatter" summarizes these effects. The central nervous system effects of muscarinic antagonists are particularly noteworthy because muscarinic ACh receptors are abundant in the brain, blockade of which may result in psychoactive effects including excitation, restlessness, sedation, confusion, hallucinations, stupor, delirium, psychosis, seizures, or coma. These alterations in sensorium associated with centrally acting muscarinic antagonists are characteristic features of central anticholinergic syndrome (known as "postoperative delirium" when it occurs after emergence from general anesthesia) and may persist well beyond the expected duration of the offending drug's metabolism. Antihistamines, tricyclic antidepressants, phenothiazines, benzodiazepines, and a variety of other medications are also associated with central anticholinergic syndrome (Table 13-4). As mentioned previously, the treatment of choice for central anticholinergic syndrome is the tertiary amine anticholinesterase physostigmine, which crosses the blood-brain barrier and increases ACh concentrations in the central nervous system. Physostigmine is most often administered in 1 or 2 mg doses to avoid producing peripheral cholinergic activity. Importantly, the duration of action of physostigmine may be shorter than that of the muscarinic antagonist. As a result, repeated treatment with physostigmine may be required if symptoms recur. Nevertheless, the drug must be used with caution because of unopposed cholinergic agonist effects in the absence of a muscarinic antagonist.

Fundamentals of Catecholamine Pharmacology

4 1 α-, β-, and dopamine-adrenergic receptor subtypes mediate the cardiovascular effects of endogenous (epinephrine, norepinephrine, dopamine) and synthetic (dobutamine, isoproterenol) catecholamines (Table 13-5). These substances stimulate β_1-adrenoceptors located on the sarcolemmal membrane of atrial and ventricular myocytes to varying degrees. Activation of β_1-adrenoceptors causes positive chronotropic (increase in heart rate), dromotropic (faster conduction velocity), inotropic (greater contractility), and lusitropic (shorter relaxation) effects. A stimulatory guanine nucleotide-binding (G_s) protein couples the β_1-adrenoceptor to the intracellular enzyme adenylyl cyclase (Fig. 13-4). Agonist occupation of the β_1-adrenoceptor accelerates

the formation of the second messenger cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). Activation of this signaling cascade has three major consequences in myocardial calcium (Ca^{2+}) homeostasis: first, greater Ca^{2+} availability for contractile activation; second, increased efficacy of activator Ca^{2+} at troponin C of the contractile apparatus; and third, faster removal of Ca^{2+} from the contractile apparatus and the sarcoplasm after contraction. The first two of these actions directly increase contractility (inotropic effect), whereas the third facilitates more rapid myocardial relaxation during early diastole (lusitropic effect). Not surprisingly, treatment of left ventricular (LV) dysfunction is the major reason why catecholamines are used during the perioperative period. The relative density and functional integrity of the β_1-adrenoceptor and its downstream signaling cascade substantially influence the clinical efficacy of catecholamines because receptor downregulation and abnormal intracellular Ca^{2+} homeostasis commonly occur in the presence of LV dysfunction.[16,17] Notably, β_2-adrenoceptors are also present in myocardium (atrial > ventricular).[18] These β_2-adrenoceptors are also linked to adenylyl cyclase through G_s proteins and act to partially preserve myocardial responsiveness to catecholamine stimulation in the presence of β_1-adrenoceptor dysfunction or downregulation.[19,20]

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13.1 Catecholamines

Table 13-3 Atropine Toxicity

Dose Range (mg)	Muscarinic Antagonist Effects
0.5-1.0	Increased heart rate; xerostomia (dry mouth); thirst; lack of sweating; mild pupillary dilation
2-5	Tachycardia; palpitations; mydriasis; cycloplegia; restlessness or confusion; inability to swallow, urinate, defecate, or sweat; hot skin
10 or greater	Profound tachycardia, mydriasis, and cycloplegia; hot, red skin; fever; hallucinations; delirium; coma; death

Adapted with permission from Brown JA, Laiken N. Muscarinic receptor agonists and antagonists. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* 12th ed. New York, NY: McGraw-Hill Medical; 2011:226.

Table 13-4 Antimuscarinic Compounds Associated with Central Anticholinergic Syndrome

Belladonna Alkaloids	***Over-the-counter***
Atropine sulfate	Asthmador—atropine-like
Scopolamine hydrobromide	Compoz—scopolamine sedation
Synthetic and Natural Tertiary Amine Compounds	Sleep Eze—scopolamine sedation
Dicyclomine antispasmodic with local anesthetic activity	Sominex—scopolamine sedation
Thiphenamil antispasmodic with local anesthetic activity	***Antiparkinson Drugs***
Procaine	Benztropine
Cocaine	Trihexyphenidyl
Cyclopentolate mydriatic	Biperiden

Quaternary Derivatives of Belladonna Alkaloids	Ethopropazine
Methscopolamine bromide—antispasmodic	Procyclidine
Homatropine methylbromide—sedative, antispasmodic	***Antipsychotic Drugs***
Homatropine hydrobromide—ophthalmic solution—mydriatic	Chlorpromazine
Synthetic Quaternary Compounds	Thioridazine
Methantheline bromide	Haloperidol
Propantheline bromide	Droperidol
Antihistamines	Promethazine
Chlorpheniramine	***Tricyclic Antidepressants***
Diphenhydramine	Amitriptyline
Plants	Imipramine
Deadly nightshade (atropine)	Desipramine
Bittersweet	***Synthetic Opioids***
Potato leaves and sprouts	Meperidine
Jimson or loco weed	Methadone
Coca plant (cocaine)	

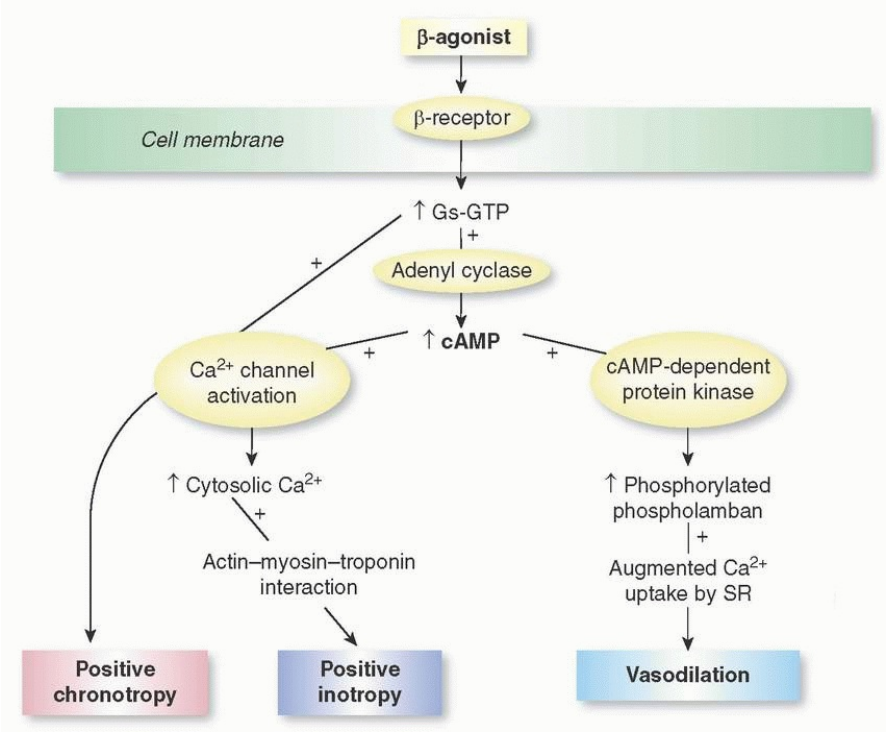
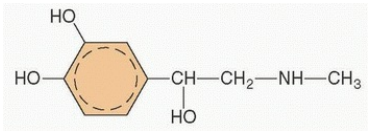
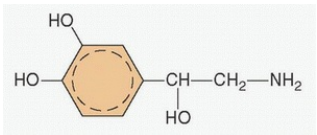
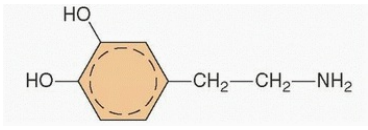
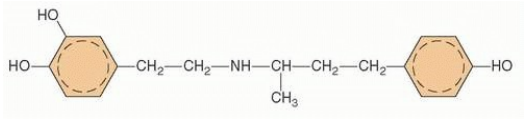
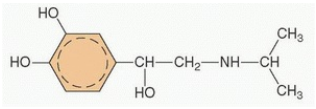
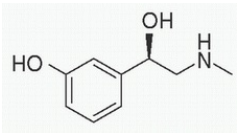


Figure 13-4 Schematic illustration of β-adrenoceptor agonist mechanism of action. (Adapted with permission from Gillies M, Bellomo R, Doolan L, et al. Bench-to-bedside review: Inotropic drug therapy after adult cardiac surgery: a systematic literature review. *Crit Care.* 2005;9:266-279.)

Table 13-5 Comparative Effects of Endogenous and Synthetic Catecholamines

Name	Chemical Structure	β_1	β_2
Epinephrine		++++	+++
Norepinephrine		+++	+
Dopamine		++++	++
Dobutamine		+++++	+++

Isoproterenol		+++++	+++++
Phenylephrine		0	0

Abbreviations: IV, intravenous; IM, intramuscular; CHF, congestive heart failure; AS, aortic stenosis; HCM, hypertrophic obstructive cardiomyopathy.

Modified from Linn KA, Pagel PS. Cardiovascular pharmacology. In: Barash PG, Cullen BF, Stoelting RK, et al., eds. *Clinical Anesthesia Fundamentals*. Philadelphia, PA: Wolters Kluwer; 2015:234-235.

5 The tissue-specific distribution of α- and β-adrenoceptor subtypes combines with differences in each catecholamine's chemical structure and its relative selectivity for adrenoceptors to determine the actions of catecholamines in other perfusion beds. This selectivity is often dose-related. Dopamine provides a particular useful (although not strictly accurate) pedagogical illustration of this principle. Lower doses of this catecholamine (<3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) predominantly stimulate dopamine subtype 1 and 2 receptors (DA_1 and DA_2, respectively) and cause splanchnic and renal arterial vasodilation. Progressively larger doses of dopamine sequentially activate β_1- (5 to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and α_1-adrenoceptors (>10 $\mu g \cdot kg^{-1} \cdot min^{-1}$), enhancing contractility and causing arterial vasoconstriction, respectively. α_1-Adrenoceptors are major regulators of vasomotor tone in arteries, arterioles, and veins. Thus, catecholamines with substantial α_1-adrenoceptor agonist activity (e.g., norepinephrine) increase systemic vascular resistance and reduce venous capacitance through arterial and venous vasoconstriction, respectively. Phospholipase-inositol 1,4,5-triphosphate signaling through an inhibitory guanine nucleotide-binding (G_i) protein

mediates this α_1-adrenoceptor vasoconstriction (Fig. 13-5). This cascade opens Ca^{2+} channels, releases Ca^{2+} from intracellular stores (sarcoplasmic reticulum and calmodulin), and activates several Ca^{2+}-dependent protein kinases. These actions act in concert to increase intracellular Ca^{2+} concentration and cause contraction of vascular smooth muscle. α_1-Adrenoceptors predominate in many vascular beds, but β_2-adrenoceptors are the most common adrenoceptor subtype in skeletal muscle. Catecholamine-induced activation of β_2-adrenoceptors produces arteriolar vasodilation through adenylyl cyclase-mediated signaling. The result of this vasodilation is increased blood flow to skeletal muscle, which facilitates the “fight or flight” response to a perceived threat.

α_1	$Dopamine_1$	Dose Range	Clinical Indications	Major Side Effects
+++++	0	IV: 0.01-0.2 μg/kg/min Bolus: 1 mg IV q 3-5 min IM(1:1,000): 0.1-0.5 mg	Shock (cardiogenic, vasodilatory) Bronchospasm Anaphylaxis Symptomatic bradycardia unresponsive to atropine/pacing	Arrhythmias Myocardial Ischemia Sudden cardiac death Hypertension Stroke
+++++	0	IV: 0.01-0.2 μg/kg/min	Shock (cardiogenic, vasodilatory)	Arrhythmias Bradycardia Peripheral ischemia Hypertension Tissue necrosis with extravasation
+++	+++++	IV: 2-20 μg/kg/min	Shock (cardiogenic, vasodilatory) Symptomatic bradycardia unresponsive to atropine/pacing	Hypertension Arrhythmias Myocardial ischemia Peripheral ischemia (high doses)
+	0	IV: 2-20 μg/kg/min	Low cardiac output (CHF, cardiogenic shock, sepsis-induced myocardial dysfunction) Symptomatic bradycardia unresponsive to atropine/pacing	Tachycardia Arrhythmias Myocardial ischemia Hypertension Hypotension
0	0	IV: 2-10 μg/kg/min	Bradyarrhythmias Denervated heart	Arrhythmias Myocardial ischemia Hypertension Hypotension
+++++	0	IV: 0.15-0.75 μg/kg/min Bolus: 0.1-0.5 mg	Hypotension with tachycardia Hypotension in AS or HCM	Reflex bradycardia Hypertension Peripheral and visceral vasoconstriction

				Tissue necrosis with extravasation

The actions of each specific catecholamine on heart rate, myocardial contractility, and LV preload and afterload combine to determine its overall effect on arterial pressure. For example, if a catecholamine acts primarily through the α_1-adrenoceptor, an increase in arterial pressure may be predicted because enhanced arterial and venous vasomotor tone increases systemic vascular resistance (greater afterload) and facilitates venous return to the heart (increased preload), respectively. In contrast, a catecholamine with primarily β-adrenoceptor activity and little or no effect on the α_1-adrenoceptor should modestly decrease arterial pressure because reductions in systemic vascular resistance (through β_2-adrenoceptor activation) offset increases in cardiac output caused by tachycardia and enhanced myocardial contractility (β_1-adrenoceptor effects). All catecholamines have the potential to cause detrimental increases in myocardial oxygen consumption in patients with flow-limiting coronary artery stenoses and may produce acute myocardial ischemia as a result. Thus, the use of a catecholamine to support LV function in a patient with heart failure and coronary artery disease should be approached with caution. For this reason, afterload reduction is usually a more prudent approach to improve cardiac output and reduce congestive symptoms in a patient with coronary artery disease complicated by heart failure.

Epinephrine

Methylation of norepinephrine by phenylethanolamine *N*-methyltransferase converts the norepinephrine into epinephrine in adrenal medullary chromaffin cells. Epinephrine is stored in

and released from specific chromaffin cells that differ from those that store norepinephrine. These epinephrine- and norepinephrine-containing chromaffin cell types appear to release their respective catecholamines somewhat selectively to differing stimuli. For example, chromaffin cells storing epinephrine are especially sensitive and release this catecholamine in response to histamine exposure, whereas nicotinic agonists cause release of norepinephrine.[21] Epinephrine exerts its major cardiovascular effects through activation of α_1-, β_1-, and β_2-adrenoceptors. Epinephrine is the quintessential positive inotropic molecule. Epinephrine stimulates β_1-adrenoceptors located on the cell membranes of sinoatrial (SA) node cells and cardiac myocytes to increase heart rate and myocardial contractility, respectively. Epinephrine-induced activation of β_1-adrenoceptors also enhances the rate and extent of myocardial relaxation. This action improves ventricular filling during early diastole. The combination of these actions on heart rate and LV systolic and diastolic function markedly increases cardiac output. For example, increases in cardiac index of 0.1, 0.7, and 1.2 L $min^{-1} \cdot m^2$ were observed during intravenous infusion of epinephrine (0.01, 0.02, and 0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in humans.[22] The initial tachycardia that occurs during administration of an intravenous infusion of epinephrine is often partially attenuated over time as baroreceptor-mediated reflexes are activated. Epinephrine is particularly useful for the treatment of acute biventricular failure during cardiac surgery because it predictably increases cardiac output. Epinephrine (0.01 to 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$) caused similar hemodynamic effects with less pronounced tachycardia compared with dobutamine (2.5 to 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in patients after coronary artery bypass graft surgery.[23] The authors recommend the use of epinephrine as the primary inotropic drug for the treatment of acute LV dysfunction after cardiopulmonary bypass because it produces very predictable increases in cardiac output compared with its synthetic derivatives. Data indicating that routine use of dobutamine in cardiac surgery adversely affects outcome support this recommendation.[24] Epinephrine also enhances cardiac output and oxygen delivery without producing deleterious tachycardia in patients with sepsis. However, epinephrine's efficacy as an inotropic drug is often limited because of the catecholamine's propensity to cause atrial or ventricular arrhythmias. Epinephrine increases conduction velocity and reduces refractory period in the AV node, His bundle, Purkinje fibers, and ventricular muscle. The positive dromotropic effect of epinephrine on AV nodal conduction may produce supraventricular tachyarrhythmias or cause pronounced increases in ventricular rate in the presence of atrial flutter or fibrillation. Either of these clinical conditions may inadvertently cause hypotension because profound tachycardia compromises coronary perfusion and LV filling time. Epinephrine may also increase the automaticity of latent pacemakers because spontaneous diastolic depolarization is enhanced. Irritability in other parts of the conduction system may also precipitate ventricular arrhythmias including premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation, especially in the presence of a pre-existing arrhythmogenic substrate (e.g., regional myocardial ischemia or infarction, cardiomyopathy).

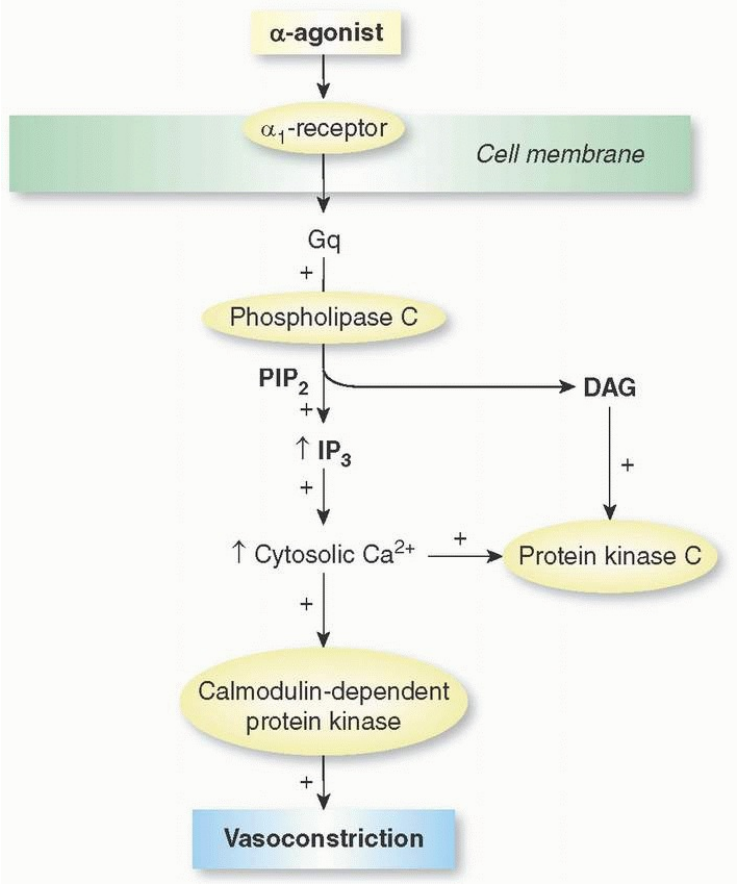


Figure 13-5 Schematic illustration of α-adrenoceptor agonist mechanism of action. (Adapted with permission from Gillies M, Bellomo R, Doolan L, et al. Bench-to-bedside review: Inotropic drug therapy after adult cardiac surgery: a systematic literature review. *Crit Care.* 2005;9:266-279.)

Epinephrine causes vasoconstriction in cutaneous, mesenteric, splenic, and renal perfusion territories because it is an α_1-adrenoceptor agonist, but the catecholamine also simultaneously vasodilates arterial blood vessels supplying skeletal muscle as a result of β_2-adrenoceptor activation.[25] Thus, epinephrine's overall effects on blood flow are dependent on the organspecific distribution of α_1- and β_2-adrenoceptors. These actions are also dose-dependent: lower doses (<0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$) of epinephrine stimulate β_2-adrenoceptors, causing vasodilation and modest declines in arterial pressure. In contrast, higher doses (>0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) of the catecholamine activate α_1-adrenoceptors, increasing systemic vascular resistance and arterial pressure. Higher doses of epinephrine also cause intense renal arterial vasoconstriction resulting from the combination of direct α_1-adrenoceptor agonist effects and indirect facilitation of renin release. The increase in arterial pressure associated with a large bolus dose (e.g., 1 mg in adults) of epinephrine improves coronary blood flow and survival during cardiopulmonary resuscitation.[26] As a result, epinephrine is the drug of choice in the American Heart Association Adult Advanced Cardiac Life Support protocols for malignant ventricular arrhythmias, pulseless electrical activity, and asystole.[27]

The venous circulation also contains a high density of α_1-adrenoceptors. As a result, epinephrine produces venoconstriction and enhances venous return to the heart (preload). Epinephrine causes vasoconstriction of the pulmonary arterial vascular smooth muscle and increases pulmonary arterial pressures through α_1-adrenoceptor activation. These actions may be especially pronounced in patients with pulmonary arterial hypertension (e.g., cor pulmonale, congenital heart diseases with left-to-right shunt). α_1- and β_2-adrenoceptors exist in the coronary circulation, but selective activation of either of these receptor subtypes does not represent the major mechanism by which epinephrine affects coronary blood flow. Instead, increases in coronary blood flow observed during administration of epinephrine occur principally because of metabolic autoregulation. Indeed, increases in myocardial oxygen consumption resulting from increases in

heart rate, contractility, preload, and afterload are responsible for coronary vasodilation. Nevertheless, epinephrine may directly constrict epicardial coronary arteries and reduce coronary blood flow in the presence of pre-existing maximal coronary vasodilation (e.g., acute myocardial ischemia distal to a severe coronary stenosis) through direct α_1-adrenoceptor stimulation.

The vasoconstrictor properties of epinephrine make it useful for several other clinical applications. Subcutaneous infiltration of epinephrine is used to substantially reduce or nearly eliminate bleeding during dental, otolaryngology, plastic surgery, and orthopedic surgery procedures. The mixture of a local anesthetic (e.g., lidocaine) with a dilute concentration of epinephrine reduces blood loss associated with tumescent anesthesia for liposuction. The vasoconstriction produced by epinephrine also substantially decreases the risk of adverse cardiovascular side effects (e.g., hypertension, arrhythmias) because the catecholamine is slowly absorbed under these circumstances. Anesthesiologists routinely use epinephrine as a vasoconstrictor to delay the absorption of local anesthetics and thereby prolong the duration of neuraxial anesthesia or peripheral nerve blocks. This effect also decreases serum anesthetic concentration and reduces the risk of systemic toxicity. Mucosal vasoconstriction resulting from inhalation of aerosolized racemic epinephrine (containing a mixture of the levo- and dextrorotary optical isomers) is frequently used to treat airway edema associated with prolonged endotracheal intubation, airway trauma, or croup. Intramuscular injection of epinephrine may be preferred to inhalation of the catecholamine in pediatric patients with severe croup because rebound edema may occur when using the latter technique as a result of the relatively short half-life of inhaled epinephrine.[28] Finally, epinephrine-induced activation of β_2-adrenoceptors in airway smooth muscle causes bronchodilation in patients with reactive airway disease. Epinephrine also decreases antigenmediated release of histamine and leukotrienes from mast cells, which makes the catecholamine useful for the treatment of bronchospasm associated with anaphylaxis.[29]

Prior administration of α- or β-adrenoceptor antagonists profoundly influences the epinephrine's cardiovascular effects. For example, epinephrine causes more pronounced increases in systemic vascular resistance and arterial pressure when administered in the presence of the nonselective β-blocker propranolol because β_2-adrenoceptor-mediated arterial vasodilation no longer opposes α_1-adrenoceptor-induced vasoconstriction. β-Blockade also competitively inhibits epinephrine-induced β_1-adrenoceptor activation. This competitive inhibition attenuates the positive chronotropic and inotropic effects of the catecholamine. Indeed, the hemodynamic effects of epinephrine may be quite similar to those of the synthetic pure α_1-adrenoceptor agonist phenylephrine (see below) in the presence of complete β_1- and β_2-adrenoceptor blockade. Conversely, epinephrine's β_2-adrenoceptor-mediated vasodilation is unmasked in the presence of α_1-adrenoceptor blockade, and the catecholamine may produce hypotension under these conditions. α_2-Adrenoceptor antagonists (e.g., cocaine) enhance the intensity and duration of action of the epinephrine's cardiovascular effects by inhibiting its reuptake.

Norepinephrine

Norepinephrine is the endogenous neurotransmitter released from postganglionic sympathetic nervous system nerve terminals. Norepinephrine activates α_1-, α_2-, and β_1-adrenoceptors, but this catecholamine has little effect on β_2-adrenoceptors, unlike its methylated derivative epinephrine. As a result of this adrenoceptor selectivity, norepinephrine predictably enhances myocardial contractility and causes intense arterial vasoconstriction. These actions dramatically increase arterial pressure while cardiac output remains relatively unchanged. In contrast, administration of a pure α_1-adrenoceptor agonist (e.g., phenylephrine) produces dose-related declines in cardiac output in normal and failing myocardium by increasing LV afterload because β_1-adrenoceptors are not stimulated and resulting increases in contractility do not occur. Unlike epinephrine, norepinephrine usually does not cause tachycardia because elevated arterial pressure activates baroreceptor-mediated reflexes, effectively balancing the direct positive chronotropic effects of β_1-adrenoceptor stimulation. In general, greater increases in diastolic arterial pressure and systemic vascular resistance occur during administration of norepinephrine compared with similar doses of epinephrine. Norepinephrine constricts venous capacitance vessels through α_1-adrenoceptor stimulation. This action increases venous return (preload), and combined with a β_1-adrenoceptor-mediated positive inotropic effect, modestly augments stroke volume despite concomitant increases in LV afterload.

Norepinephrine is most often used for treatment of refractory hypotension resulting from pronounced vasodilation. Norepinephrine is an established treatment in patients with septic shock[30] that is unresponsive to volume administration or other vasoactive medications because the catecholamine increases arterial pressure, cardiac index, and urine output. Norepinephrine, most often in combination with nitric oxide scavenger methylene blue, is also useful for the management of vasoplegic syndrome.[31] This hypotensive state is associated with low systemic vascular resistance and frequently occurs during or after prolonged cardiopulmonary bypass in patients undergoing cardiac surgery. The potent vasoconstrictor vasopressin has largely supplanted norepinephrine in this clinical setting. Norepinephrine increases coronary perfusion pressure in patients with severe coronary artery disease, but the catecholamine also dramatically increases myocardial oxygen consumption and may produce acute myocardial ischemia in the presence of flowlimiting coronary stenoses despite the improvement in diastolic arterial pressure. Norepinephrine may also cause spasm of internal mammary or radial artery grafts used during coronary artery surgery as a result of activation of α_1-adrenoceptors. Ventricular and supraventricular arrhythmias are sometimes observed during administration of norepinephrine, but the arrhythmogenic potential of norepinephrine is less than that of epinephrine. As a result, substitution of norepinephrine for epinephrine may be appropriate when hemodynamically significant atrial or ventricular arrhythmias are present.

Norepinephrine stimulates pulmonary arterial α_1-adrenoceptors and causes dose-related increases in pulmonary arterial pressures that may precipitate right ventricular (RV)

dysfunction or failure because the RV is relatively intolerant to acute increases in afterload compared with the more muscular, thicker walled LV. An inhaled selective pulmonary vasodilator (e.g., nitric oxide, prostacyclin) may help to attenuate norepinephrine's direct pulmonary vasoconstrictor effects when the catecholamine is used in patients with pulmonary hypertension and depressed myocardial contractility. Alternatively, lower doses of norepinephrine may be administered directly through a left atrial catheter in patients with LV failure and pulmonary hypertension because metabolism in peripheral tissues reduces the quantity of norepinephrine that is returned to the pulmonary vasculature through the venous circulation. This selective left atrial route of norepinephrine administration enhances coronary perfusion pressure while simultaneously increasing LV contractility. These actions may decrease biventricular filling

pressures and increase cardiac output. When arterial pressure is normal or modestly reduced, norepinephrine causes dosedependent decreases in hepatic, skeletal muscle, splanchnic, and renal blood flow through α_1-adrenoceptor-induced vasoconstriction. However, norepinephrine increases perfusion pressure and blood flow to these vascular beds when arterial pressure is profoundly reduced. Nevertheless, sustained reductions in renal, mesenteric, and peripheral vascular blood flow represent a major limitation of prolonged use of norepinephrine. Activation of renal dopamine receptors with low-dose dopamine or the selective DA_1 agonist fenoldopam to partially counteract the deleterious actions of norepinephrine on renal blood flow may preserve renal perfusion and urine output but most likely does not reduce the incidence or severity of acute kidney injury in patients with hypotension. Norepinephrine should be administered through a central venous catheter to avoid the possibility of tissue necrosis from extravasation.

Dopamine

Dopamine is the biochemical precursor of norepinephrine. The catecholamine activates several adrenergic and dopaminergic receptor subtypes in a dose-related fashion. Lower doses (below 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) selectively activate DA_1 receptors to dilate renal, mesenteric, and splenic arterial blood vessels and increase renal and splanchnic blood flow. Lower doses of dopamine also reduce norepinephrine release from pre- and postganglionic sympathetic neurons through a DA_2-receptor-mediated mechanism. As a result of these actions, lower doses of dopamine modestly decrease arterial pressure. Moderate doses (3 to 8 $\mu g \cdot kg^{-1} \cdot min^{-1}$) of dopamine activate both α_1- and β_1-adrenoceptors, resulting in elevated arterial pressure and positive inotropic effects. In contrast, high doses (in excess of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) of dopamine act primarily on α_1-adrenoceptors to increase arterial pressure through arteriolar vasoconstriction. Unfortunately, this dose-response description of dopamine pharmacodynamics is overly simplistic because differences in receptor density and regulation, drug interactions, and patient variability cause a wide, often unpredictable range of clinical responses[32] even in healthy individuals.[33] For example, it was once presumed that low doses of dopamine provided renal protective effects through DA_1-receptor-mediated increases in renal blood flow. However, this hypothesis was subsequently not supported because even low doses of dopamine are capable of producing simultaneous α_1-and β_1-adrenoceptor activation that may attenuate or abolish the catecholamine's intended renal dopaminergic effect. Conversely, renal blood flow and urine output may be preserved (and are certainly not reduced) during administration of higher doses of dopamine because DA_1 receptors continue to be activated despite a predominant α_1-adrenoceptor agonist effect. Varied responses such as these may explain why the results of several clinical trials indicated that dopamine does not consistently provide renal protective effects despite improvements in renal perfusion and urine output. A meta-analysis of 61 clinical trials involving 3,359 patients demonstrated that low-dose dopamine transiently increased urine output, but the catecholamine did not reduce the incidence or severity of renal dysfunction or prevent mortality.[34] Thus, the use of low-dose dopamine to maintain or enhance renal function and prevent acute kidney injury is no longer recommended.[35]

View Quicktime Video

13.2 Dopamine

Dopamine is still occasionally used as a positive inotropic medication in patients with acute LV dysfunction, although the authors prefer to use more potent catecholamines that have more predictable pharmacodynamic profiles (e.g., epinephrine, norepinephrine) with or without a cardiac phosphodiesterase fraction III inhibitor (e.g., milrinone) for this purpose in their practices. Dopamine increases myocardial contractility through activation of β_1-adrenoceptors. Dopamine also stimulates arterial and venous α_1-adrenoceptors, increasing LV afterload and enhancing venous return, respectively. As a result of these combined actions on α_1- and β_1-adrenoceptors, dopamine increases arterial pressure and cardiac output. The use of dopamine for the treatment of hypotension in the presence of depressed contractility is limited to some degree in patients with pre-existing pulmonary arterial hypertension or heart failure with elevated LV filling pressures. For example, right atrial, mean pulmonary arterial, and pulmonary capillary occlusion pressures were greater in patients undergoing cardiac surgery receiving dopamine compared with dobutamine despite producing similar increases in cardiac output. Dopamine may also cause more pronounced tachycardia than epinephrine in cardiac surgery patients. An arterial vasodilator (e.g., sodium nitroprusside) may be used to blunt dopamine-induced increases in LV afterload and thereby further enhance cardiac output. However, inotrope-vasodilators (e.g., milrinone, levosimendan) are more commonly used for this purpose in modern anesthesia practice than this older “dopamine plus nitroprusside (‘dopride’)” strategy. Like epinephrine and norepinephrine, dopamine directly increases myocardial oxygen consumption and may cause or worsen myocardial ischemia in the presence of hemodynamically significant coronary stenoses.

Dobutamine

Commercial preparations of the synthetic catecholamine dobutamine contain two stereoisomers (- and +), both of which stimulate β-adrenoceptors, but these (-) and (+) stereoisomers cause opposing agonist and antagonist effects on α_1-adrenoceptors, respectively.[36] As a result, dobutamine is a potent stimulator of β-adrenoceptors, but the drug has little effect on α_1-adrenoceptors when it is administered at infusion rates less than 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. This unique pharmacology allows dobutamine to enhance myocardial contractility and simultaneously reduce arterial vasomotor tone through β_1- and β_2-adrenoceptor activation, respectively. These actions combine to markedly improve LV-arterial coupling, enhance myocardial efficiency, and increase cardiac output in the presence or absence of LV dysfunction.[37] The favorable effects of dobutamine on mechanical matching between the LV and the arterial vasculature also partially explain the declines in mitral regurgitation observed when dobutamine is administered to patients with dilated cardiomyopathy and increased LV filling pressures.[38] The dobutamine (-) isomer progressively stimulates the α_1-adrenoceptor as infusion rates increase above 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. This action mitigates the magnitude of vasodilation resulting from β_2-adrenoceptor activation and effectively preserves LV preload, afterload, and arterial pressure. The α_1-adrenoceptor agonist effect of higher doses of dobutamine also serves to blunt the baroreceptor reflex-mediated tachycardia that might otherwise occur. Nevertheless, dobutamine often increases heart rate by direct β_1-adrenoceptor-mediated positive chronotropic and dromotropic effects. In fact, dobutamine produced significantly higher heart rates than epinephrine at equivalent values of cardiac index in patients after coronary artery surgery.[23] Dobutamine directly increases myocardial oxygen consumption and may cause acute myocardial ischemia in patients with flow-limiting coronary stenoses. This is the underlying principle behind dobutamine stress echocardiography as a diagnostic tool for the detection of coronary artery disease because regional wall motion abnormalities in the affected coronary perfusion territories occur in response to the myocardial oxygen supply-demand

mismatch during transient infusion of the drug.[39] Conversely, dobutamine often reduces heart rate in patients with heart failure because increases in cardiac output and oxygen delivery improve tissue perfusion and reduce chronically elevated sympathetic nervous system tone. Dobutamine may also favorably decrease myocardial oxygen consumption in the failing heart because stimulation of β_2-adrenoceptors decreases LV preload and afterload and, consequently, LV end-diastolic and end-systolic wall stress, respectively.

Dobutamine modestly decreases pulmonary arterial pressures and pulmonary vascular resistance through β_2-adrenoceptor stimulation. Thus, dobutamine may be a useful positive inotropic drug in intensive care unit patients with pulmonary arterial hypertension.[40] As previously mentioned, dopamine, in contrast to dobutamine, activates α_1-adrenoceptors in the pulmonary arterial and venous capacitance vessels, and these effects increase pulmonary arterial pressures and LV preload, respectively. As a result, dobutamine may be preferred over dopamine in heart failure patients with elevated pulmonary vascular resistance and LV filling pressures. However, this dobutamineinduced pulmonary vasodilation has the potential to exacerbate ventilation-perfusion mismatch, increase transpulmonary shunt, and contribute to relative hypoxemia. Dobutamine may also improve renal perfusion by increasing cardiac output, but unlike dopamine, the drug does not directly activate DA_1 receptors to cause renal arterial vasodilation. Unfortunately, several clinical trials demonstrated that use of dobutamine was linked to an increased incidence of major adverse cardiac events including mortality in patients with decompensated heart failure despite the theoretical beneficial cardiovascular effects of the drug.[41],[42] Dobutamine also produced adverse events in patients undergoing cardiac surgery.[24] As a result of these and other compelling data, the authors have personally eliminated the use of dobutamine for positive inotropic support in patients with LV dysfunction undergoing cardiac surgery. Nevertheless, dobutamine remains a useful drug for the treatment of depressed myocardial contractility in patients with sepsis.[43]

Isoproterenol

Isoproterenol is a nonselective β-adrenoceptor agonist synthetic catecholamine derived from dopamine. Isoproterenol has a low affinity for and does not exert activity at the α-adrenoceptor. As a result, isoproterenol increases heart rate and myocardial contractility and decreases arterial pressure through β_1- and β_2-adrenoceptor agonist effects, respectively. Historically, isoproterenol was used for "pharmacologic pacing" in patients with symptomatic bradyarrhythmias or AV conduction block (e.g., Mobitz type II second-degree block, third-degree block) because of the drug's positive chronotropic effects. Isoproterenol was also used during cardiac transplantation to increase heart rate and enhance myocardial contractility in the deneverated donor organ. However, transcutaneous or transvenous pacing has largely replaced the catecholamine for heart rate control in modern practice, especially in view of the drug's propensity to precipitate adverse supraventricular and ventricular tachyarrhythmias.[44] Isoproterenol was previously used to treat RV dysfunction resulting from severe pulmonary arterial hypertension because the drug reduces pulmonary vascular resistance by stimulating β_2-adrenoceptors in pulmonary arterial vascular smooth muscle, but selective inhaled pulmonary vasodilators (e.g., nitric oxide, prostaglandin I_2) are more effective and are associated with fewer adverse side effects. Thus, although the clinical applicability of isoproterenol is quite limited at present, the comparison of the pharmacology of isoproterenol with other catecholamines merits continued discussion.

Isoproterenol causes β_2-adrenoceptor-mediated arteriolar vasodilation in renal, mesenteric, splenic, and skeletal muscle circulations. These actions reduce systemic vascular resistance and decrease arterial pressure. Isoproterenol causes direct positive chronotropic and dromotropic effects and increases heart rate because of β_1-adrenoceptor activation. Tachycardia also occurs because hypotension stimulates baroreceptor reflex-mediated increases in heart rate. Isoproterenol is a positive inotropic drug, but cardiac output may not increase because tachycardia interferes with LV filling dynamics and β_2-adrenoceptor-mediated venodilation decreases LV preload. For example, isoproterenol, unlike dobutamine, did not increase cardiac output in patients undergoing coronary artery or valve replacement surgery. Predictably, the hemodynamic effects of isoproterenol cause dose-related increases in myocardial oxygen consumption. The synthetic catecholamine also reduces coronary perfusion pressure and decreases diastolic filling time. These alterations in myocardial oxygen supply-demand relations may contribute to the development of acute myocardial ischemia or cause subendocardial necrosis, even in the absence of coronary artery disease. Thus, isoproterenol may be especially deleterious in patients with flow-limiting coronary stenoses.

Selective β_2-Adrenoceptor Agonists

A number of short- and long-acting selective β_2-adrenoceptor agonists, including metaproterenol, albuterol, salmeterol, and fenoterol, are currently in clinical use for treatment of asthma and chronic obstructive pulmonary disease. A hydroxyl substitution on the phenyl ring or a large moiety attached to the amino group of a catecholamine's basic chemical structure increases the molecule's relative β_2-adrenoceptor affinity. These drugs stimulate β_2-adrenoceptors in bronchial smooth muscle to produce bronchodilation, reduce airway resistance, and improve obstructive symptoms. Reductions in histamine and leukotriene release from pulmonary mast cells, and improvements in mucociliary function may also contribute to beneficial effects of selective β_2-adrenoceptor agonists in patients with reactive airway disease.[45] To minimize the systemic side effects of β_2-adrenoceptor activation (e.g., tremor, anxiety, restlessness), the drugs are usually aerosolized and administered using a metered-dose inhaler. However, the β_2-adrenoceptor selectivity of these drugs progressively decreases and β_1-adrenoceptor-mediated adverse effects (e.g., tachycardia, arrhythmias) become more apparent as larger doses are used. Terbutaline is another β_2-adrenoceptor agonist that is administered subcutaneously or intramuscularly and may be useful in the management of status asthmaticus.

Fenoldopam

Fenoldopam mesylate is an intravenous selective DA1-receptor agonist that does not exert activity at α- or β-adrenoceptors.[35] The drug dilates mesenteric, splenic, and renal arterioles, increases renal blood flow, decreases renal vascular resistance, reduces systemic vascular resistance, improves creatinine clearance, and promotes both natriuretic and diuretic effects. Fenoldopam was initially developed as an antihypertensive medication because of its actions as a vasodilator,[46] but the drug may also be capable of protecting the kidney against radiographic contrast-induced

nephropathy, presumably by virtue of enhanced renal blood flow.[47],[48] This potential to block renal injury, particularly in the presence of hypotension or pre-existing kidney damage, prompted intense investigation of fenoldopam as a possible renal protective agent. For example, a large meta-analysis based primarily on small single center studies suggested that fenoldopam may reduce the risk of acute tubular necrosis, the need for renal replacement therapy, and overall mortality in patients with or at risk for acute kidney injury.[49] Unfortunately, large randomized controlled clinical trials have failed to support these promising early results. Fenoldopam did not provide renal protection against contrast-induced nephropathy.[50] Similarly, fenoldopam did not decrease the need for dialysis in intensive care unit patients with early acute tubular necrosis,[51] nor did the DA_1-receptor agonist reduce the requirement for renal replacement therapy or 30-day mortality in patients with acute kidney injury undergoing cardiac surgery.[52] Thus, despite the fact that fenoldopam is a potent direct renal vasodilator and promotes increased urine output, the drug does not appear to exert clinically meaningful protection against renal injury. Intravenous fenoldopam has a rapid onset of action as an antihypertensive medication. The drug undergoes hepatic metabolism and is excreted in the urine. The elimination half-life of fenoldopam is approximately 5 minutes. Unlike the findings with intravenous nitrovasodilators (see below), tolerance to fenoldopam's antihypertensive effects does not appear to occur. Rebound hypertension has also not been observed with abrupt discontinuation of the drug. The most common adverse effects of fenoldopam are related to its effects as a vasodilator and include hypotension, tachycardia, flushing, dizziness, headache, tachycardia, and nausea.

Sympathomimetics

Ephedrine

The sympathomimetic drug ephedrine exerts both direct and indirect actions on adrenoceptors. Endocytosis of ephedrine into α_1- and β_1-adrenoceptor presynaptic postganglionic nerve terminals displaces norepinephrine from the synaptic vesicles. The displaced norepinephrine is then released to activate the corresponding postsynaptic receptors to cause arterial and venous vasoconstriction and increased myocardial contractility, respectively. This indirect action is the ephedrine's predominant pharmacologic effect. Indeed, ephedrine's initial cardiovascular effects resemble those of epinephrine because dose-related increases in heart rate, cardiac output, and systemic vascular resistance are observed. However, ephedrine is less potent than epinephrine, and the indirect acting sympathomimetic's duration of action is longer than that of the endogenous catecholamine. Ephedrine also directly stimulates β_2-adrenoceptors, which limits the increases in arterial pressure that occur as a result of α_1-adrenoceptor activation. Tachyphylaxis to ephedrine's hemodynamic effects occurs with repetitive administration of the drug because presynaptic norepinephrine stores are quickly depleted and ephedrine is released from synaptic vesicles as a false neurotransmitter instead. In contrast, tachyphylaxis does not occur with epinephrine because the endogenous catecholamine directly stimulates α- and β-adrenoceptors independent of norepinephrine displacement and release. Notably, drugs that block the ephedrine uptake into adrenergic nerves (e.g., cocaine) and those that deplete norepinephrine reserves (e.g., reserpine) predictably attenuate the cardiovascular effects of ephedrine. The most common clinical use of ephedrine during anesthesia is treatment of acute decreases in arterial pressure concomitant with bradycardia. Ephedrine was previously used for the treatment of hypotension in laboring parturients because the drug increases uterine blood flow, but phenylephrine may be preferred in this setting because ephedrine crosses the placenta and may cause fetal acidosis.[53]

Phenylephrine

The chemical structure of phenylephrine is similar to epinephrine: unlike the endogenous catecholamine, the sympathomimetic drug does not contain a hydroxyl group on the phenyl ring. As a result of this minor structural difference, phenylephrine almost exclusively stimulates α_1-adrenoceptors to increase venous and arterial vasomotor tone while exerting little or no effect on β-adrenoceptors. In contrast to ephedrine, phenylephrine acts directly on the α_1-adrenoceptor and is not dependent on presynaptic norepinephrine displacement to produce its cardiovascular effects. Phenylephrine constricts venous capacitance vessels and causes cutaneous, skeletal muscle, mesenteric, splenic, and renal vasoconstriction. These actions increase LV preload and afterload and cause dose-related increases in arterial pressure. Predictably, baroreceptor reflex-mediated decreases in heart rate also occur. Cardiac output usually remains relatively constant when LV function is normal, but cardiac output may decline when LV function is impaired[54] because failing myocardium is more sensitive to acute increases in afterload.[55] Phenylephrine also increases pulmonary artery pressures through pulmonary arterial vasoconstriction and greater venous return. Unlike endogenous or synthetic catecholamines, phenylephrine is not arrhythmogenic. Intravenous boluses or infusions of phenylephrine are most often used for treatment of hypotension in the presence of normal or elevated heart rate.

α_1-Adrenoceptor Antagonists

6 On the basis of the previous discussion, it should be readily apparent that blockade of the α_1-adrenoceptor in arterial and venous vascular smooth muscle causes vasodilation by inhibiting the actions of endogenous catecholamines and other sympathomimetic amines at this receptor subtype. For this reason, α_1-adrenoceptor blockers were previously used for the treatment of essential hypertension, but β-blockers, ACE inhibitors, angiotensin II receptor blockers (ARBs), Ca^{2+} channel blockers, diuretics, and nitrates have largely replaced these drugs for this clinical indication in modern practice. α_1-Adrenoceptor antagonists (e.g., prazosin) are certainly very effective antihypertensive medications, but many patients complained that the side effect profile, including debilitating orthostatic hypotension, baroreceptor reflex-mediated tachycardia[56] with or without palpitations, nasal congestion, and fluid retention, was intolerable during chronic use of these drugs. The presence of α_1-adrenoceptor blockade also has the potential to cause unopposed β_1- and β_2-adrenoceptor activity. For example, epinephrine will activate only β_1- and β_2-adrenoceptors because the α_1-adrenoceptor agonist effects of the catecholamine are inhibited. As a result, epinephrine produces pronounced tachycardia (a β_1 effect) and severe hypotension (activation of β_2 receptors causing arterial and venous vasodilation) when administered in the presence of an α_1-adrenoceptor blocker. Similarly, norepinephrine and ephedrine only activate β_1-adrenoceptors because their α_1-adrenoceptor agonist actions are inhibited. The pure α_1-agonist phenylephrine also exerts little or no effect

as a vasoconstrictor under these conditions. The response of a given vascular bed to an α_1-adrenoceptor antagonist is dependent on its intrinsic level of vasoconstriction, as blood vessels with higher vascular smooth muscle tone will generally be more responsive to α_1-adrenoceptor blockade.

Phenoxybenzamine is an orally administered, relatively nonselective α-adrenoceptor antagonist that binds irreversibly to α_1- and α_2-adrenoceptors (the ratio of selectivity for these receptor subtypes is approximately 100:1). Because phenoxybenzamine's actions at a-adrenoceptors are irreversible, synthesis of new receptors is required to reverse the drug's effects as a vasodilator. Phenoxybenzamine's prolonged half-life after oral administration also contributes to its sustained actions at the α-adrenoceptor. Phenoxybenzamine is used almost exclusively to normalize arterial pressure before surgery in patients with pheochromocytoma.[57] The slow onset of α-adrenoceptor blockade produced by phenoxybenzamine occurs because the molecule requires structural modification to become pharmacologically active. As a result, several weeks of treatment may be required to obtain adequate control of arterial pressure. Restoration of normal intravascular volume status is also an important goal of phenoxy-benzamine therapy because hypovolemia resulting from elevated serum norepinephrine and epinephrine concentrations contributes to hemodynamic instability during pheochromocytoma resection. Subsequent addition of a β-adrenoceptor antagonist also helps in achieving these goals and also serves to protect the myocardium from the adverse effects of chronic catecholamine stimulation. These combined interventions facilitate greater cardiovascular stability during pheochromocytoma resection, which is usually associated with additional release of norepinephrine and epinephrine into the circulation during tumor manipulation. The most prominent side effect of phenoxybenzamine therapy is orthostatic hypotension, which may be especially severe in the presence of pre-existing hypertension or hypovolemia. Vasopressin may be required to treat refractory hypotension associated with phenoxybenzamine overdose.

The competitive α_1- and α_2-adrenoceptor antagonist phentolamine is also used in patients with pheochromocytoma. In contrast to phenoxybenzamine, the effects of phentolamine are reversible (half-life less than 10 minutes) and new receptor synthesis is not required to restore α-adrenoceptor activity and vascular smooth muscle tone. Phentolamine is a potent intravenous vasodilator that rapidly decreases arterial pressure, but in doing so, also causes baroreceptor reflex-mediated tachycardia. Blockade of cardiac α_2-adrenoceptors by phentolamine may contribute to the development of arrhythmias. Phentolamine also exerts antihistamine and cholinergic activity, the latter of which may produce abdominal cramping and diarrhea. Because the drug causes hypotension and tachycardia, phentolamine is relatively contraindicated and should only be used with extreme caution in patients with flow-limiting coronary artery stenoses. Phentolamine is occasionally used as a local vasodilator to prevent tissue necrosis when iatrogenic extravasation of a vasoconstrictor (e.g., norepinephrine, phenylephrine) has occurred. The α-adrenoceptor antagonist may also be effective when treating refractory hypertension associated with clonidine withdrawal or tyramine exposure in patients receiving a monoamine oxidase inhibitor.

Unlike phenoxybenzamine and phentolamine, prazosin is a relatively selective antagonist of α_1-adrenoceptors (α_1 to α_2 ratio of approximately 1,000:1) that causes arterial and venous vasodilation. α_2-Adrenoceptor modulation of norepinephrine release from postganglionic sympathetic neurons remains intact. As a result, baroreceptor reflex-mediated tachycardia is substantially attenuated after administration of prazosin. Nevertheless, orthostatic hypotension is an important clinical side effect of prazosin when the drug is used for the treatment of hypertension. Prazosin undergoes hepatic metabolism. The drug also increases the ratio of high- to low-density lipoproteins. In contrast with ACE inhibitors, prazosin does not improve survival in patients with heart failure and the drug is no longer recommended for this clinical indication as a result. Other α_1-

adrenoceptor antagonists (e.g., terazosin, doxazosin, tamsulosin) are used for the treatment of benign prostatic hyperplasia because the prostate contains a large number of α_{1A}-adrenoceptors.[58] Patients who are treated with these medications occasionally present for surgery, and anesthesiologists should be aware that anesthetic-induced vasodilation might be exacerbated in the presence of these urologic α_1-adrenoceptor antagonists.

α_2-Adrenoceptor Agonists: Clonidine and Dexmedetomidine

7 The α_2-adrenoceptor agonists clonidine and dexmedetomidine are commonly used by anesthesiologists and pain medicine specialists for sedation, anxiolysis, and analgesia.[59,60] Clonidine binds to α_2-adrenoceptors and inhibits norepinephrine release from presynaptic postganglionic sympathetic neurons. α_2-Adrenoceptor agonists block sympathetic nerve traffic through pre- and post-synaptic mechanisms in the central nervous system and also inhibit spinal presynaptic sympathetic nerve transmission. Clonidine is a partial α_2-adrenoceptor agonist with relative selectivity for α_2- versus α_1-receptors of approximately 200:1. Because of its sympatholytic effects, clonidine was originally used for the treatment of hypertension. Activation of α_2-adrenoceptors in the vasomotor center, attenuation of peripheral norepinephrine release from postganglionic sympathetic neurons, and stimulation of central nervous system imidazoline receptors are postulated mechanisms for the antihypertensive effect of clonidine.[61,62] Clonidine blunts centrally mediated sympathetic nervous system tone, decreases serum norepinephrine and norepinephrine concentrations, and reduces activation of the renin-angiotensin-aldosterone axis. In addition, clonidine stimulates parasympathetic nervous system activity, which, when combined with withdrawal of sympathetic tone, produces bradycardia. Unlike other antihypertensive medications, clonidine does not affect baroreceptor-mediated reflex control of heart rate.[63] The α_2-adrenoceptor agonist is generally not associated with orthostatic hypotension when used in patients with hypertension, unlike α_1-antagonists or ACE inhibitors. Nevertheless, hypotension and bradycardia may occur when large doses of the drug are administered. These effects are easily reversed with conventional vasoactive medications.

Clonidine continues to be used as an antihypertensive medication, but the drug also reduces volatile and intravenous anesthetic requirements, blunts the hemodynamic responses to laryngoscopy and endotracheal intubation, promotes intraoperative cardiovascular stability, partially attenuates the sympathetic stress response associated with surgery, and decreases postoperative tissue oxygen requirements.[64,65,66] Clonidine and other α_2-adrenoceptor agonists including dexmedetomidine were shown to reduce the risk of myocardial ischemia and infarction and decrease perioperative mortality in patients undergoing major vascular or cardiac surgery, in a meta-analysis of 23 controlled trials in which more than 3,395 patients were enrolled.[67] These anti-ischemic actions were presumably related to the drug's sympatholytic effects, which reduce myocardial oxygen consumption. Clonidine augments the effects of local

anesthetics and opioids and increases their duration of action when used for neuraxial and regional anesthesia.[68] As a result, clonidine decreases the incidence and severity of side effects associated with local anesthetics and opioids because the quantities of these latter drugs required for anesthesia and analgesia are reduced. Clonidine is effective as a postoperative analgesic and also has well-documented utility in the treatment of chronic regional pain syndrome and neuropathic pain. The sedative and anxiolytic effects of clonidine are attributed to activation of α_2-adrenoceptors in the locus coeruleus. Notably, clonidine does not substantially inhibit respiratory drive in the presence or absence of opioids despite the α_2-adrenoceptor agonist's sedative effect.[69] Thus, clonidine's sedative-analgesic effects may be exploited without undo concern about the potential for respiratory depression. Hyperglycemia may occur in patients treated with clonidine because the α_2-adrenoceptor agonist inhibits insulin release. This side effect may be especially important in patients with poorly controlled diabetes mellitus. Finally, anesthesiologists may occasionally encounter patients who are receiving clonidine to mitigate withdrawal symptoms associated with treatment of a substance abuse disorder.[70]

Discontinuation of clonidine may be necessary during the perioperative period if a patient is unable to ingest oral medications, but abrupt withdrawal of the α_2-adrenoceptor agonist often results in severe hypertension associated with tachycardia, headache, anxiety, tremor, and diaphoresis. Under these circumstances, invasive monitoring of arterial pressure in an intensive care unit setting and treatment of hypertension with other intravenous medications may be necessary until oral clonidine therapy can be resumed. β-Blockers should not be used alone under such circumstances because unopposed α_1-adrenoceptor stimulation causes profound vasoconstriction, thereby worsening the hypertensive emergency. Alternatively, transdermal clonidine may be used to mitigate or prevent drug withdrawal-induced hypertensive emergency in those patients who are unable to consume the medication. It is important to note that transdermal clonidine requires approximately 48 hours after initial application to achieve therapeutic serum concentrations.

3 Dexmedetomidine is approximately sevenfold more selective for the α_2-adrenoceptor (α_2 to α_1 ratio of 1,600:1) and has a substantially shorter context-sensitive half-life than clonidine. These characteristics make an intravenous infusion of dexmedetomidine useful for sedation, amnesia, and analgesia in the operating room and intensive care unit.[71,72] Like clonidine, dexmedetomidine reduces anesthetic requirements during general, neuraxial, and regional anesthesia; decreases heart rate, arterial pressure, and plasma catecholamine concentrations; attenuates intraoperative cardiovascular lability; and does not cause clinically significant respiratory depression. This latter feature is especially beneficial in the setting of elective fiberoptic intubation or weaning from mechanical ventilation. Dexmedetomidine's relative preservation of respiratory drive and its lack of effects on electrophysiologic monitoring make the α_2-adrenoceptor agonist useful for functional neurosurgery.[73] Dexmedetomidine exerts neuroprotective effects against cerebral ischemia and hypoxia; this neuroprotection appears to be related to a direct cytoprotective effect.[74] Dexmedetomidine also facilitates perioperative care of obese patients with obstructive sleep apnea and those undergoing bariatric surgery because the drug provides analgesia, reduces opioid requirements, and does not substantially depress respiration.[75] When used as a sedative in the intensive care patients, dexmedetomidine reduced the incidence of delirium, the duration of mechanical ventilation, the length of intensive care unit stay, and mortality compared with midazolam.[76] Dexmedetomidine may be associated with hypothermia because the drug lowers the threshold body temperature at which compensatory thermoregulation mechanisms are activated.

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13.3 Dexmedetomidine

β-Adrenoceptor Antagonists (β-Blockers)

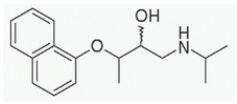
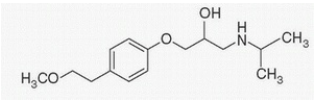
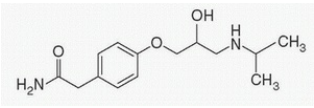
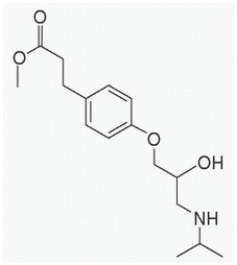
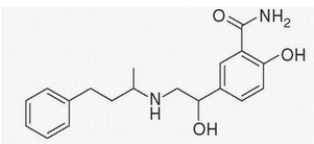
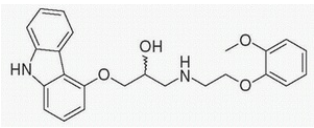
Many of the cardiovascular effects of β-adrenoceptor antagonists (more commonly called “β-blockers”) may be anticipated based on the previous discussion of catecholamines. The peer-reviewed literature describing the actions, uses, and potential limitations of β-blockers is exhaustive. It is not the authors' intention to review this literature in detail; instead, we wish to highlight the major effects and clinical applications of the most ubiquitous drugs in cardiovascular pharmacology. β-Blockers produce important anti-ischemic effects and are a first-line therapy for patients with ST- and non-ST-segment elevation, myocardial infarction in the absence of cardiogenic shock, hemodynamically significant bradyarrhythmias, or reactive airway disease. These medications have been repeatedly shown to reduce morbidity and mortality associated with myocardial infarction in a large number of clinical trials. β-Blockers bind to β_1-adrenoceptors and inhibit the actions of circulating catecholamines and norepinephrine released from postganglionic sympathetic neurons. As a result, heart rate and myocardial contractility are reduced. The decrease in heart rate produced by β-blockers prolongs diastole, increases coronary blood flow to the LV, enhances coronary collateral perfusion to ischemic myocardium, and improves oxygen delivery to the coronary

microcirculation. These combined effects serve to reduce myocardial oxygen demand while simultaneously increasing supply. β-Blockers have also been shown to inhibit platelet aggregation. This latter action is particularly important during acute myocardial ischemia or evolving myocardial infarction because platelet aggregation at the site of an atherosclerotic plaque may worsen a coronary stenosis or produce acute occlusion of the vessel. β-Blockers are very effective for the treatment of essential hypertension, produce antiarrhythmic effects through negative chronotropic actions, and have well-established roles in the treatment of heart failure, hypertrophic obstructive cardiomyopathy, aortic dissection, thyrotoxicosis, pheochromocytoma, and migraine headache prophylaxis. Topical β-blockers are also used for treatment of open-angle glaucoma. Perhaps, of most relevance to anesthesiologists, perioperative administration of β-blockers has been shown to reduce the incidence of nonfatal myocardial infarction in patients undergoing noncardiac surgery.[77],[78] These drugs are specifically recommended for patients with documented or multiple risk factors for myocardial ischemia,[79] but not those without convincing evidence of coronary artery disease.[80],[81]

Propranolol is the prototypical β-blocker against which all other medications in this pharmacologic class are compared (Table 13-6). Propranolol and other β-blockers are chemically related to isoproterenol and contain an aromatic moiety linked to the ethanolamine group, the latter of which allows interaction with the β-adrenoceptor. Additions to the molecule's aromatic group determine the degree of β_1-adrenoceptor specificity. All β-blockers have a chiral center; the negative enantiomer of each drug is biologically active. The relative selectivity of β-blockers for β_1- and β_2-adrenoceptors, their lipid solubility, and the presence or absence of intrinsic sympathomimetic ability (e.g., partial stimulation of the β_1-adrenoceptor), myocardial membrane stabilizing activity, and additional cardiovascular actions combine with each drug's pharmacokinetic effects to distinguish

individual β-blockers from one another. The ability to prevent isoproterenol-induced increases in heart rate defines each β-blocker's potency (propranolol is considered the standard in these determinations). Propranolol is a “first-generation” (non-selective) β-blocker that competitively inhibits both β_1- and β_2-adrenoceptors, whereas metoprolol, atenolol, and esmolol are classified as “second-generation” β-blockers because these drugs are selective for the β_1-adrenoceptor. Notably, this β_1-adrenoceptor selectivity is relative because larger doses of second-generation β-blockers inhibit both β_1- and β_2-adrenceptors. “Third-generation” β-blockers exert other cardiovascular effects in addition to their actions at β-adrenoceptors. For example, labetalol blocks α_1-adrenoceptors; carvedilol exerts antioxidant and anti-inflammatory actions; bucindolol has intrinsic sympathomimetic effects because it is a partial agonist of β_1-adrenoceptors; and nebivolol produces nitric oxide-mediated vasodilation through its actions on vascular endothelium.

Table 13-6 Comparative Effects of β-blockers

Name	Chemical Structure	Selectivity β_1	Selectivity β_2	α_1	Plasma Half-life (hrs)	Intrinsic Sympathomimetic Activity	Membrane Stabilizing Activity	Lipid Solubility	Metabolism
Propranolol		+	+	0	3-4	0	+	+++	Liver
Metoprolol		+	0	0	3-4	0	0	++	Liver
Atenolol		+	0	0	6-9	0	0	+	Renal
Esmolol		+	0	0	0.15	0	0	+	RBC esterase
Labetalol		+	+	+	6	+	0	+	Liver
Carvedilol		+	+	+	2-8	0	+	+++	Liver

RBC, red blood cell.

The reductions in heart rate and myocardial contractility produced by β-blockers are more pronounced in the presence of increased sympathetic nervous system tone (e.g., surgical stress, exercise, heart failure) because vagal activity is usually the predominant factor regulating cardiovascular homeostasis during basal conditions. Nonselective β-blockers initially reduce cardiac output as a result of negative chronotropic and inotropic effects concomitant with arterial vasoconstriction mediated through blockade of vascular smooth muscle β_2-adrenoceptors and compensatory sympathetic stimulation of α_1-adrenoceptors. The initial increase in systemic vascular resistance that occurs with a nonselective β-blocker gradually declines during long-term administration.[82] Selective β_1-blockers with or without α_1-adrenoceptor antagonist activity, and those with direct vasodilator effects, generally reduce systemic vascular resistance and preserve cardiac output to varying degrees despite simultaneous depression of myocardial contractility. β-Blockers are used extensively for the treatment of hypertension, but the precise mechanisms by which β-blockers that do not have specific additional vasodilating properties are able to reduce arterial blood pressure remain to be clearly defined (Fig. 13-6). Stimulation of β_1-adrenoceptors in renal juxtaglomerular cells by the sympathetic postganglionic neurons causes renin secretion and activates the renin-angiotensin-aldosterone axis (see below). Many β-blockers inhibit this renin release, but their antihypertensive effects usually occur before plasma renin concentrations decline.[83] Similarly, some β-blockers also do not substantially affect renin metabolism and yet are quite effective at reducing arterial pressure in hypertensive patients. It is also unlikely that β-blockers cause antihypertensive effects through a decrease in centrally mediated sympathetic nervous system tone because drugs with markedly different lipid solubility are equally effective at decreasing arterial pressure. β-Blockers most likely do not favorably modulate postganglionic sympathetic neuron norepinephrine release despite the presence of presynaptic β-adrenoceptors that are known to stimulate release of the neurotransmitter. Clearly, selective β-blockers that do not affect β_2-adrenoceptor viability ("second-generation") and those that inhibit α_1-adrenoceptors or produce vasodilation through other mechanisms also decrease arterial pressure (Fig. 13-6).[84] Nevertheless, nonselective β-blockers such as propranolol are valuable antihypertensive medications independent of these alternative vasodilating characteristics.

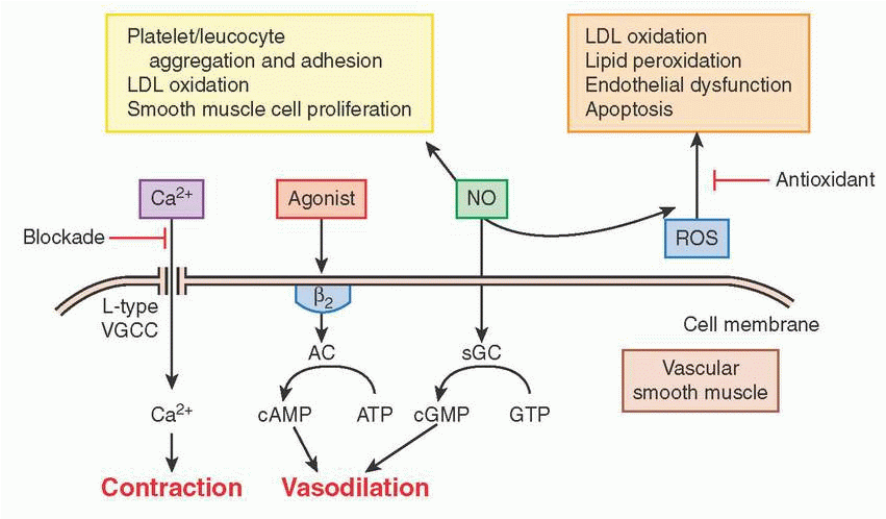


Figure 13-6 Schematic illustration of potential mechanism by which β-blockers produce vasodilation; abbreviations: VGCC, voltage-gated Ca^{2+} channel; AC, adenylyl cyclase; NO, nitric oxide; sGC, soluble guanylyl cyclase; ROS, reactive oxygen species; LDL, low-density lipoprotein. (Modified with permission from Toda N. Vasodilating β-adrenoceptor blockers as cardiovascular therapeutics. Pharmacol Ther, 2003, 100:215-234. Copyright 2003 Elsevier Inc. All rights reserved.)

β-Blockers have been a mainstay in the pharmacologic treatment of acute myocardial ischemia and infarction since their introduction into clinical practice in the 1960s. As mentioned previously, β-blockers directly reduce myocardial oxygen consumption and improve coronary perfusion, thereby enhancing myocardial oxygen supply-demand relations and decreasing ischemic burden. These actions reduce the magnitude of myocardial necrosis, preserve LV systolic function, attenuate the development of malignant ventricular arrhythmias, decrease mortality, and improve long-term functional capacity. The results supporting the use of β-blockers in acute myocardial infarction are among the most convincing data ever published in the medical literature. Many placebo-controlled randomized doubleblind clinical trials demonstrated unequivocally that β-blockers are not only effective for treatment of acute myocardial infarction but also substantially decrease the risk of developing a subsequent infarction in patients with coronary artery disease.[85],[86] Indeed, the estimated overall reduction in mortality associated with use of β-blockers in myocardial infarction is approximately 25%.[87] β-Blockers also have well-established efficacy for the chronic treatment of heart failure. The use of β-blockers in heart failure was initially viewed with skepticism because administration of a drug that further depresses myocardial contractility would appear to be counterintuitive. However, sympathetic nervous system tone is chronically elevated in heart failure, and this excessive sympathetic activity produces a series of alterations in

β_1-adrenoceptor density and function, intracellular signal transduction, contractile protein expression, and Ca^{2+} homeostasis that promote mitochondrial dysfunction, stimulate myocyte apoptosis (programmed cell death), cause pathologic ventricular remodeling, and accelerate disease progression.[88],[89] Clinical trials demonstrated that β-blockers significantly decrease mortality in patients with heart failure independent of disease severity.[90] In fact, some large randomized studies were halted before completion because patients with moderate to severe heart failure receiving β-blockers had markedly improved mortality compared with those treated with placebo.[91] β-Blockers mitigate clinical symptoms, improve exercise tolerance, reduce the need for and duration of subsequent hospitalization, and decrease the risk of sudden cardiac death in patients with heart failure.[92]

The electrophysiologic effects of β-blockers make these drugs quite useful for the treatment of tachyarrhythmias. β-Blockers reduce SA node automaticity, inhibit the activity of subsidiary ectopic pacemakers, decrease impulse conduction velocity through atrial conduction pathways, prolong conduction time through the AV node, and increase the AV node's refractory period. Both β_1- and β_2-adrenoceptors mediate these negative chronotropic and dromotropic effects.[20] Some β-blockers also exert membrane-stabilizing activity that may theoretically contribute to their antiarrhythmic efficacy, but these "quinidine-like" actions are most likely only of clinical relevance when a β-blocker overdose has occurred. β-Blockers are used to reduce ventricular rate in patients with sinus tachycardia, atrial fibrillation or flutter, supraventricular tachycardia, and re-entrant tachyarrhythmias (e.g., Wolff-Parkinson-White, Lown-Ganong-Levine). β-Blockers inhibit tachycardia in response to laryngoscopy and endotracheal intubation. β-Blockers also attenuate baroreceptor-mediated reflex sinus tachycardia in response to vasodilator therapy. For example, administration of a β-blocker mitigates the reflex tachycardia associated with an α_1-adrenoceptor antagonist used to reduce arterial pressure in pheochromocytoma. β-Blockers also attenuate the development of cardiomyopathy resulting from elevated catecholamine concentrations in this disease. When combined with intravenous vasodilator therapy (e.g., sodium nitroprusside, clevidipine), the negative chronotropic and inotropic effects of β-blockers reduce heart rate and proximal ascending aortic shear stress in acute Stanford type A (Debakey type I or II) aortic dissection. Analogously, β-blockers reduce the risk of aortic dissection and the rate of ascending aortic dilatation in patients with Marfan's syndrome by decreasing pulsatile

hydraulic forces on the proximal aortic root.[93] β-Blockers decrease heart rate and inhibit the development of tachyarrhythmias in hyperthyroidism and thyroid storm, in part by preventing the peripheral conversion of thyroxine to its more active triiodothyronine form. As a result, β-blockers are useful adjuncts to propylthiouracil in the treatment of hyperthyroidism. β-Blocker-induced declines in heart rate concomitant with depression of myocardial contractility substantially reduce dynamic LV outflow tract pressure gradient and the magnitude-associated mitral regurgitation while improving symptoms in patients with hypertrophic obstructive cardiomyopathy.[94]

Topical β-blockers (e.g., timolol, betaxolol) are used for the treatment of open-angle glaucoma. These drugs reduce aqueous humor production but do not affect pupil size or accommodation, unlike topical anticholinergic medications. It is important to recognize that these topical β-blockers may be systemically absorbed and thus, may exert adverse cardiovascular or pulmonary side effects. As a result, topical β-blockers may be relatively contraindicated in patients with symptomatic bradyarrhythmias or bronchospastic lung disease. A role for β-blockers in prophylaxis against migraine headache is well established, but the mechanism for this beneficial effect remains unclear.[95] β-Blockers may also be useful for reducing sympathetically mediated symptoms, including palpitations, tachycardia, and tremor, associated with performance situations that provoke anxiety (e.g., public speaking, oral examinations). Similarly, β-blockers may also be helpful in controlling sympathetic nervous system activation that occurs with drug withdrawal in patients with substance use disorders.

β-Blockers are associated with a number of important adverse effects. Despite the well-established beneficial effects of β-blockers in patients with heart failure, the negative inotropic effects of these drugs may worsen heart failure symptoms and lead to further decompensation in some patients with severe LV dysfunction. Abrupt withdrawal of a β-blocker after long-term treatment may produce myocardial ischemia and infarction or cause sudden cardiac death in susceptible patients with critical coronary artery stenoses. Because of the electrophysiologic effects of β-blockers, second- or third-degree heart block may occur in patients with pre-existing AV conduction abnormalities or those treated with other negative dromotropic drugs (e.g., diltiazem, verapamil).[96] Nonselective β-blockers inhibit β_2-adrenoceptors in arterial vascular smooth muscle. The resulting vasoconstriction may occasionally worsen vascular insufficiency in patients with peripheral vascular disease or precipitate Raynaud's phenomenon in susceptible individuals. Nevertheless, β-blockers remain a mainstay in the treatment of patients with peripheral vascular disease because the vast majority of these patients also have clinically significant coronary artery disease that substantially increases their risk of myocardial ischemia, arrhythmias, and mortality. Propranolol and other first-generation β-blockers inhibit bronchial β_2-adrenoceptors and may cause potentially fatal bronchoconstriction in patients with asthma or chronic obstructive pulmonary disease. Long-term use of β_1-blockers (e.g., atenolol) for the treatment of hypertension, myocardial ischemia and infarction, or heart failure must be approached with caution in patients with reactive airway disease because the β_1-selectivity of these drugs is not absolute and suitable alternative medications are available (e.g., Ca^{2+} channel blockers, nitrates, ACE inhibitors) to manage these conditions. Nevertheless, a selective β_1-adrenoceptor antagonist may be advantageous in some patients with coronary artery disease who also suffer from chronic obstructive pulmonary disease.[97] β-Blockers also interfere with carbohydrate and lipid metabolism. Endogenous catecholamines stimulate glycogenolysis, lipolysis, and gluconeogenesis, promoting the release of glucose into the circulation when hypoglycemia is present. Nonselective β-blockers may inhibit this physiologic response to and recovery from hypoglycemia, especially in patients with type I diabetes mellitus. Nonselective β-blockers also attenuate the sympathetically mediated tremor, tachycardia, and anxiety associated with hypoglycemia. Thus, nonselective β-blockers may be relatively contraindicated in patients with poorly controlled diabetes who often develop hypoglycemic episodes, and drugs with β_1-selectivity may be preferred in this setting.[98]

Propranolol

As mentioned previously, propranolol is the prototypical nonselective β-blocker. Available in oral and intravenous forms, propranolol inhibits β_1- and β_2- but not α_1-adrenoceptors and possesses some degree of membrane stabilization activity at higher doses, but does not exert intrinsic sympathetic activity. The medication is highly lipophilic, easily absorbed from the stomach, and undergoes extensive first-pass hepatic metabolism. A high degree of variability between patients is observed

in propranolol metabolism between patients. Liver disease and reductions in hepatic blood flow, but not renal impairment, delay the drug's metabolism and require dose adjustment. Propranolol is used for treatment of hypertension and symptomatic coronary artery disease. Despite a relatively short half-life (approximately 4 hours), propranolol can most often be administered using a twice-per-day dosing regimen because of a persistent antihypertensive effect. Several weeks of propranolol treatment are often required to achieve optimal reduction in arterial pressure. Inhibition of tachycardia during exercise indicates adequate β-blockade. Intravenous propranolol was used for treatment of tachyarrhythmias, but esmolol is preferred for this indication in current clinical practice because of its short half-life. The landmark Beta-Blocker Heart Attack Trial demonstrated that propranolol therapy substantially decreases mortality (7.2% compared with 9.8%) in patients with acute myocardial infarction.[99] Use of propranolol has gradually decreased with the widespread application of other β_1-selective blockers and thirdgeneration drugs with other cardiovascular actions.

Metoprolol

Metoprolol is relatively selective for β_1-adrenoceptors but has no intrinsic sympathetic or membrane stabilization activity. The drug is available in oral and intravenous forms. Like propranolol, oral metoprolol is rapidly absorbed, but the drug does undergo first-pass hepatic metabolism by cytochrome P450 2D6 that limits its initial availability. The kidney excretes less than 10% of the drug in its original form. Metoprolol's half-life of 3 to 4 hours allows twice-per-day dosing in patients with normal metabolism, but an extended release form is also available that allows once-daily administration. The half-life of metoprolol is doubled in patients who are poor cytochrome P450 2D6 metabolizers; these individuals are approximately fivefold more likely to develop adverse side effects after oral metoprolol administration.[100] Metoprolol is commonly used for treatment of hypertension, angina pectoris, acute myocardial infarction, and chronic heart failure.[101]

Atenolol

8 Like metoprolol, atenolol is a selective inhibitor of β_1-adrenoceptors and does not possess intrinsic sympathetic or membrane stabilization activity. The drug has a longer half-life (6 to 9 hours) than metoprolol that facilitates a daily dosing regimen. The liver does not metabolize atenolol, most of which is excreted in its original form by the kidney. As a result, the dose of atenolol must be reduced in patients with moderate to severe renal insufficiency. The lack of first-pass hepatic metabolism reduces variability in plasma atenolol concentrations between patients after oral administration.[102] Similar to other β-blockers, atenolol is used for the treatment of hypertension, coronary artery disease, acute myocardial infarction, and heart failure.

Esmolol

Esmolol is a relatively selective β_1-blocker. The chemical structure of esmolol is very similar to that of propranolol and metoprolol, but esmolol contains an additional methylester group that facilitates the drug's rapid metabolism via hydrolysis by red blood cell esterases, resulting in an elimination half-life of approximately 9 minutes. The quick onset and rapid metabolism of esmolol makes the drug very useful for the treatment of acute tachycardia and hypertension during surgery. Esmolol is most often administered as an intravenous bolus, which causes almost immediate dose-related decreases in heart rate and myocardial contractility; arterial pressure most often falls as a result of these direct negative chronotropic and inotropic effects. Esmolol is often used to attenuate the sympathetic nervous system response to laryngoscopy, endotracheal intubation, or surgical stimulation, particularly in patients with known or suspected coronary artery disease who may be at risk for acute myocardial ischemia. Esmolol is also useful for rapid control of heart rate in patients with supraventricular tachyarrhythmias (e.g., atrial fibrillation, atrial flutter). Finally, esmolol effectively blunts the sympathetically mediated tachycardia and hypertension that occur shortly after the onset of seizure activity during electroconvulsive therapy. Because esmolol does not appreciably block β_2-adrenoceptors due to its relative β_1-selectivity, hypotension is more commonly observed after administration of this drug compared with other

nonselective β-blockers.

Labetalol

Labetalol is composed of four stereoisomers that inhibit α- and β-adrenoceptors to varying degrees.[103] One of the four stereoisomers is an α_1-adrenoceptor antagonist, another is a nonselective β-blocker, and the remaining two do not appreciably affect adrenergic receptors. The net effect of this mixture is a drug that selectively inhibits α_1-adrenoceptors while simultaneously blocking β_1- and β_2-adrenoceptors in a nonselective manner. The intravenous formulation of labetalol contains a ratio of α_1- to β-blockade of approximately 1:7. Blockade of the α_1-adrenoceptor causes arteriolar vasodilation and decreases arterial pressure through a reduction in systemic vascular resistance. This property makes the drug very useful for the treatment of perioperative hypertension. Despite its nonselective β-blocking properties, labetalol is also a partial β_2-adrenoceptor agonist; this latter characteristic also contributes to vasodilation. Labetalol-induced inhibition of β_1-adrenoceptors decreases heart rate and myocardial contractility. Stroke volume and cardiac output are essentially unchanged as a result of the combined actions of labetalol on α_1- and β_2-adrenoceptors. Unlike other vasodilators, labetalol produces vasodilation without triggering baroreceptor reflex tachycardia because the drug blocks anticipated increases in heart rate mediated through β_1-adrenoceptors. This latter action is beneficial for the treatment of hypertension in the setting of acute myocardial ischemia. Labetalol is also useful for controlling arterial pressure without producing tachycardia in patients with hypertensive emergencies and those with acute aortic dissection. Labetalol has been shown to attenuate the sympathetic nervous system response to laryngoscopy and endotracheal intubation, although the drug's relatively long elimination half-life (approximately 6 hours) limits its utility in this setting.

Carvedilol

Carvedilol is another third-generation β-blocker that inhibits β_1-, β_2-, and α_1-adrenoceptors.[104] Like labetalol, the drug causes arterial vasodilation because it is an α_1-adrenoceptor antagonist. The drug is a membrane stabilizer but lacks intrinsic sympathomimetic activity. Carvedilol exerts important antioxidant and antiinflammatory effects: the drug not only suppresses production of reactive oxygen species, but it also is a scavenger of these free radical intermediates. The antioxidant and anti-inflammatory

actions of carvedilol inhibit the uptake of deleterious reduced low-density lipoproteins into coronary vascular endothelium and protect myocardium against ischemia-reperfusion injury, in part by attenuating recruitment, chemotaxis, and activation of cytotoxic neutrophils.[105] Carvedilol is commonly used in the treatment of hypertension, stable angina pectoris, and acute myocardial infarction, but the drug has been shown to be particularly efficacious in patients with heart failure. Several large clinical trials provided convincing evidence that carvedilol improves LV function, reverses or slows the progression of pathologic LV remodeling, decreases the need for and the duration of subsequent hospitalization, and substantially reduces mortality in chronic heart failure resulting from a variety of underlying causes including coronary artery disease.[106] In fact, the beneficial effects of carvedilol appear to be greater than those of metoprolol in heart failure, and several experts have opined that carvedilol should be the preferred therapeutic option in this clinical setting.[107] Carvedilol is very lipophilic, is nearly entirely absorbed after oral administration, and, similar to propranolol and metoprolol, undergoes extensive first-pass hepatic oxidative metabolism via cytochrome P450 2D6 with little or no dependence on the kidney for elimination.

Phosphodiesterase Inhibitors

The phosphodiesterases are structurally related enzymes that hydrolyze the second messengers cAMP and cGMP and terminate their physiologic effects in a variety of tissues. At least seven different phosphodiesterase isoform subtypes have been identified. Inhibitors of these enzymes enhance the intracellular effects of cAMP and cGMP by preventing their metabolism. The phosphodiesterase inhibitors currently in clinical use are somewhat isoenzyme-selective at lower doses, but this selectivity is lost when higher doses of these medications are used. Myocardium and vascular smooth muscle contain the type III phosphodiesterase isoenzyme (PDE III), which is bound to the sarcoplasmic reticulum and cleaves cAMP to adenosine monophosphate (AMP).[108] Selective inhibition of cardiac PDE III by bipyridine compounds such as milrinone and inamrinone alters intracellular Ca^{2+} regulation to enhance myocardial contractility without affecting catecholamine release or activation of beta$_1$-adrenoceptors. PDE III inhibitors increase cAMP concentration, enhance protein kinase A activity, and phosphorylate voltagedependent Ca^{2+} channels[109] and phospholamban, the major sarcoplasmic reticulum regulatory protein.[110] These actions combine to increase transsarcolemmal Ca^{2+} influx into the cardiac myocyte and promote Ca^{2+}-induced Ca^{2+} release from its sarcoplasmic reticulum, thereby exerting a positive inotropic effect because larger quantities of Ca^{2+} are available for contractile activation. Inhibition of cAMP metabolism also stimulates greater Ca^{2+} uptake into the sarcoplasmic reticulum. As a result, PDE III inhibitors enhance the rate and extent of myocardial relaxation. This positive lusitropic effect serves to improve diastolic function in many patients with heart failure.

9 PDE III inhibitors cause pronounced arterial and venous vasodilation by blocking cGMP-metabolism and facilitating the actions of this second messenger in vascular smooth muscle. The proclivity of PDE III inhibitors to simultaneously enhance contractility and cause vasodilation defines these medications as “inodilators.” PDE III inhibitors cause relatively greater vasodilation than drugs with β_2-adrenoceptor agonist activity, including dobutamine and isoproterenol. This reduction in LV afterload increases cardiac output, improves LV-arterial coupling, and enhances mechanical efficiency. Intravenous or inhalational administration of PDE III inhibitors also reduces pulmonary vascular resistance, an action that may be particularly helpful in patients with pulmonary arterial hypertension who are undergoing cardiac surgery or transplantation.[111,112] However, this pulmonary vasodilation is capable of increasing intrapulmonary shunt and contributing to the development of hypoxemia. PDE III inhibitors also dilate venous capacitance vessels and reduce preload. Notably, decreases in preload and afterload resulting from administration of a PDE III inhibitor often lead to reductions in myocardial oxygen consumption in patients with heart failure despite simultaneous positive inotropic, lusitropic, and chronotropic effects.[113] In general, mean arterial pressure is either maintained or may be modestly reduced during administration of PDE III inhibitors provided that intravascular volume is adequately supplemented because increases in cardiac output are capable of compensating for reductions in afterload.

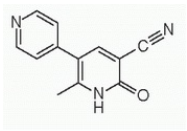
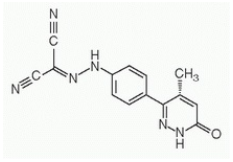
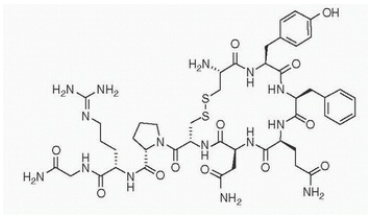
PDE III inhibitors cause increases in heart rate that are less pronounced than those observed during administration of catecholamines. Indeed, a selective β_1 adrenoceptor antagonist may abolish the positive chronotropic effects of a PDE III inhibitor without depressing the latter drug's positive inotropic effect. PDE III inhibitors may precipitate the development of malignant ventricular arrhythmias because these drugs increase intracellular cAMP and Ca^{2+} concentrations.[114] PDE III inhibitors block platelet aggregation, suppress neointimal hyperplasia associated with endothelial injury, and attenuate the proinflammatory effects of cardiopulmonary bypass.[115] In addition, these drugs dilate native epicardial coronary arteries and arterial bypass conduits.[116] As a result, PDE III inhibitors have the potential to exert important anti-ischemic effects in patients with coronary artery disease undergoing CABG surgery. The efficacy of PDE III inhibitors is reduced in the failing heart, but not to the extent observed with β_1 adrenoceptor agonists. Thus, PDE III inhibitors will continue to enhance myocardial contractility despite concomitant β adrenoceptor downregulation and dysfunction.[113] This pharmacologic property stimulated the conduct of a number of large clinical trials designed to evaluate the utility of orally administered PDE III inhibitors for the treatment of chronic severe heart failure. Although PDE III inhibitors did enhance cardiac performance and improve apparent quality of life in these studies, the drugs also significantly increased mortality resulting from ventricular arrhythmias and sudden cardiac death.[117] Hence, while the use of PDE III inhibitors is contraindicated for the treatment of chronic heart failure, these drugs continue to be of central importance for the treatment of acute LV dysfunction during cardiac surgery and in the intensive care unit. The authors often use the combination of a PDE III inhibitor and a β_1-adrenoceptor agonist when weaning patients with pre-existing LV systolic dysfunction from cardiopulmonary

bypass because these drugs produce synergistic effects on cAMP-mediated intracellular signaling.

Milrinone (Table 13-7) and inamrinone are PDE III inhibitors that have been used extensively for inotropic support during and after cardiac surgery. Milrinone is 15- to 20-fold more potent than the chemically similar compound inamrinone. Milrinone enhances myocardial contractility and causes arterial and venous vasodilation, thereby improving the likelihood of successful weaning of patients with poor LV function from cardiopulmonary bypass.[118] The pharmacokinetics and pharmacodynamics of milrinone were extensively studied in patients undergoing cardiac surgery[119] and those in the intensive care unit.[120] Milrinone loading doses of 25 or 50 $\mu g \cdot kg^{-1}$ and infusion rates ranging between 0.375 and 0.75 $\mu g \cdot kg^{-1} \cdot min^{-1}$ are useful for increasing cardiac output and oxygen delivery in these clinical settings. Inamrinone was the first clinically used phosphodiesterase III inhibitor and exerted cardiovascular effects that were almost identical to those

of milrinone, but use of the drug for the treatment of LV dysfunction was abandoned because of its propensity to cause profound thrombocytopenia during prolonged use.[121]

Table 13-7 Comparative Effects of Milrinone, Levosimendan, and Vasopressin

Name	Chemical Structure	Mechanism of Action	Dose Range	Clinical Indications	Major Side Effects
Milrinone		PDE III inhibition	Load: 25-50 µg/kg IV: 0.375-0.75 µg/kg/min	Acute LV dysfunction	Arrhythmias Myocardial ischemia Sudden cardiac death Hypertension Stroke
Levosimendan		Myofilament Ca^{2+} sensitization PDE III Inhibition K_{ATP} channel opener	Load: 12-24 µg/kg IV: 0.05-0.2 µg/kg/min	Acute LV dysfunction Heart failure	Tachycardia Hypotension
Vasopressin		V_1 (vascular smooth muscle) and V_2 (renal collecting tubules) agonist	IV: 0.01-0.1 U/min	Shock (vasodilatory, cardiogenic) Cardiac arrest	Arrhythmias Hypertension Myocardial ischemia Reduced cardiac output Peripheral ischemia Splanchnic vasoconstriction

Abbreviations: IV, intravenous; LV, left ventricular; Ca^{2+}, calcium; PDE, phosphodiesterase; K_{ATP}, adenosine triphosphate-sensitive potassium channel.

Modified from Linn KA, Pagel PS. Cardiovascular pharmacology. In: Barash PG, Cullen BF, Stoelting RK, et al., eds. *Clinical Anesthesia Fundamentals*. Philadelphia, PA: Wolters Kluwer; 2015:234-235.

Levosimendan

Myofilament Ca^{2+} sensitizers are positive inotropic, vasodilating drugs that enhance myocardial contractility by increasing the Ca^{2+} sensitivity of the contractile apparatus.[122] Levosimendan (Table 13-7) is the only drug in this class that is currently available, although a number of other myofilament Ca^{2+} sensitizers were previously studied in clinical trials. Levosimendan is used extensively in Europe for short-term treatment of heart failure[123] and for inotropic support in patients undergoing cardiac surgery.[124] However, use of the drug in the United States is relatively limited because it remains unclear whether levosimendan provides any clinically meaningful unique advantages over conventional therapy.[125] Levosimendan was initially touted as a treatment for acute decompensation of chronic heart failure that would decrease morbidity and mortality, but the myofilament Ca^{2+} sensitizer did not reduce the incidence of death or major adverse cardiac events compared with dobutamine.[126] Intermittent ambulatory treatment with levosimendan also did not improve functional capacity or quality of life in patients with advanced heart failure.[127] Levosimendan produced rapid improvement of symptoms in patients with acute decompensated heart failure, but the drug also increased the risk of cardiovascular-related complications.[123] As a result of these and other recent clinical trials, the future of levosimendan as a treatment for heart failure is uncertain.

Levosimendan exerts its positive inotropic and vasodilator actions through three major mechanisms.[128] First, levosimendan binds to troponin C (TnC) and stabilizes the Ca^{2+}-bound conformation of the regulatory protein in a Ca^{2+}-dependent manner. This action prolongs the interaction between actin and myosin filaments and enhances the rate and extent of myocyte contraction to increase myocardial contractility. The Ca^{2+}-dependence of levosimendan-TnC binding prevents relaxation abnormalities that would otherwise be expected to occur. Second, levosimendan is a potent PDE III inhibitor that produces positive inotropic and lusitropic effects and causes systemic, pulmonary, and coronary vasodilation. Finally, levosimendan opens ATP-dependent K^+(K_{ATP}) channels, which contribute to the drug's vasodilator properties and may also produce the additional benefit of myocardial protection against reversible[129] and irreversible[130] ischemic injury. Levosimendan decreases LV filling pressures, mean arterial pressure, and pulmonary and systemic vascular resistances and increases cardiac output in patients with heart failure. The modest reductions in arterial pressure observed with levosimendan are similar to those produced by milrinone and usually respond to volume administration. Levosimendan also improves LV-arterial coupling and mechanical efficiency, while causing only minimal increases in heart rate and myocardial oxygen consumption. Similar to the findings in the setting of heart failure, levosimendan also improves cardiac performance concomitant with reductions in pulmonary capillary occlusion pressure and systemic vascular resistance in patients with normal and depressed

LV systolic function undergoing cardiac surgery.[131] Levosimendan has a biologically active metabolite (OR-1896) that most likely contributes to the parent drug's more

prolonged hemodynamic effects compared with catecholamines or PDE III inhibitors.[132]

Digitalis Glycosides

The search for new drugs that chronically enhance myocardial contractility in failing heart has been astonishingly disappointing despite decades of intense cardiovascular pharmacology research.[133] Digitalis glycosides continue to be the only currently available class of positive inotropic drugs for oral treatment of mild to moderate heart failure, and these medications have been used for centuries. Digitalis glycosides are naturally occurring substances found in several plant species including “foxglove” (*Digitalis purpurea*). The most commonly prescribed digitalis glycosides are digoxin and digitoxin, but a number of related compounds are also used clinically. Digitalis glycosides enhance contractile function, but this positive inotropic effect is relatively minor when compared with other drugs used for the treatment of acute LV dysfunction. Digitalis glycosides selectively bind to the α-subunit of the sarcolemmal Na^+-K^+ ATPase on its extracellular surface and reversibly inhibit the enzyme.[134] An increase in extracellular K^+ concentration partially inhibits this digitalis-Na^+-K^+ ATPase binding. As a result, administration of K^+ is capable of reversing digitalis toxicity resulting from hypokalemia. Inhibition of sarcolemmal Na^+-K^+ ATPase indirectly increases Ca^{2+} availability, thereby enhancing myocardial contractility. The Na^+-K^+ ATPase enzyme normally trades three Na^+ ions (intracellular to extracellular) for two K^+ ions (extracellular to intracellular) against their corresponding cation concentration gradients. Inhibition of this energy-dependent ion exchange produces modestly increases intracellular Na^+ concentration, which reduces Ca^{2+} extrusion from the myoplasm by the sarcolemmal Na^+-Ca^{2+} exchanger. The additional Ca^{2+} is stored in the sarcoplasmic reticulum and then released during the next contraction. In contrast to other drugs that increase myocardial contractility, tachyphylaxis to the positive inotropic effects of digitalis glycosides does not occur. The mechanism of action of digitalis glycosides is similar to that implicated for the Treppe (“staircase”) phenomenon (see Chapter 12), in which a rapid increase in heart rate causes a delay in Na^+-K^+ ATPase activity, leading to a transient increase in intracellular Na^+ concentration and enhanced contractile force mediated by favorable Na^+-Ca^{2+} exchange.

The increase in myocardial contractility produced by digitalis glycosides is associated with declines in LV preload and afterload, LV wall tension, and myocardial oxygen consumption in the failing heart. Heart rate remains unchanged. Because digitalis glycosides augment contractility and improve cardiac output, these drugs reduce the chronically elevated sympathetic nervous system activity that is a characteristic feature of heart failure. Reductions in norepinephrine concentrations and consequently, declines in LV afterload, also occur in response to this withdrawal of sympathetic tone. The decrease in sympathetic nervous system activity observed with digitalis glycosides is also related to the direct actions of these drugs on cardiac baroreceptors. These combined actions play important roles in reducing morbidity and mortality in patients with heart failure.[135] However, digitalis-induced inhibition of Na^+-K^+ ATPase also causes profound alterations in electrophysiology (e.g., SA and AV nodes, conduction pathways, His-Purkinje fibers) because the enzyme maintains normal resting membrane potential. Withdrawal of sympathetic and increases in parasympathetic nervous system activity further modulate the direct electrophysiologic effects of digitalis glycosides. Thus, it is not surprising that digitalis glycosides often cause a wide variety of arrhythmias including sinus bradycardia or arrest, AV conduction delays, and second- or third-degree heart block. Notably, toxic levels of digitalis glycosides may paradoxically increase sympathetic nervous system tone and precipitate the development of ventricular tachyarrhythmias. Digitalis glycosides have a low therapeutic ratio and narrow margin of safety. As a result, mortality resulting from arrhythmias is directly related to a digitalis drug's plasma concentration. Digitalis glycosides are most often used for management of supraventricular tachyarrhythmias with rapid ventricular response during the perioperative period because the drugs prolong conduction time in the AV node.

Vasopressin

10 Vasopressin (antidiuretic hormone; Table 13-7) is a peptide hormone released from the posterior pituitary that regulates water reabsorption in the kidney and exerts potent hemodynamic effects independent of adrenoceptors. Vasopressin receptors consist of three subtypes (V_1, V_2, and V_3), all of which are five-subunit helical membrane proteins coupled to G proteins. Vasopressin's cardiovascular effects are predominately mediated through V_1 receptors, which are located in the cell membrane of vascular smooth muscle.[136] Activation of the V1 receptor subtype stimulates phospholipase C and triggers hydrolysis of inositol 4,5-bisphosphate (PIP_2) to inositol 1,4,5-triphosphate (IP_3) and diacyl glycerol (DAG). These second messengers increase intracellular Ca^{2+} concentration and produce contraction of the vascular smooth muscle cell. V_2 receptors are present on renal collecting duct cells and, when activated, increase reabsorption of free water, whereas V_3 receptors are located in the pituitary gland itself and act as autacoid modulators.

Along with the sympathetic nervous system and renin-angiotensin-aldosterone axis, endogenous vasopressin plays an essential role in the maintenance of arterial pressure. Exogenous administration of vasopressin does not substantially affect arterial pressure in conscious, healthy patients because activation of central V_1 receptors in the area postrema enhances baroreceptor reflex-mediated inhibition of efferent sympathetic nervous outflow that counterbalances the elevated system vascular resistance resulting from V_1-induced arterial vasoconstriction. In contrast, vasopressinergic mechanisms are essential for maintaining arterial pressure under conditions in which sympathetic nervous system or renin-angiotensin-aldosterone axis dysfunction is present. Indeed, exogenous administration of vasopressin has been shown to effectively support arterial pressure when a relative vasopressin deficiency exists (e.g., catecholamine-refractory hypotension, vasodilatory shock, sepsis, cardiac arrest). ACE inhibitors and ARBs used to treat hypertension also affect autonomic nervous system and renin-angiotensin-aldosterone axis function. Intraoperative hypotension that is relatively refractory to administration of catecholamines or sympathomimetics has been repeatedly described in patients who are treated with these medications. General or neuraxial anesthesia also reduces sympathetic nervous system tone, resulting in decreased plasma stress hormone concentrations including vasopressin. Under these circumstances, administration of vasopressin activates V_1 vascular smooth muscle receptors and rapidly increases arterial pressure during anesthesia by causing arterial vasoconstriction.

Vasopressin therapy has been shown to reduce mortality associated with acute vasodilatory states such as anaphylaxis. In addition, infusion of vasopressin is indicated for the treatment of severe hypotension after prolonged cardiopulmonary bypass in patients who are otherwise unresponsive to phenylephrine or norepinephrine (vasoplegia).

Vasopressin is a useful drug for the treatment of sepsis and cardiac arrest. Vasodilation that is refractory to fluid resuscitation combined with a relative deficiency of endogenous vasopressin is a characteristic feature of sepsis. Inadequate sympathetic nervous system and renin-angiotensin-aldosterone axis responses to hypotension are also present in sepsis. Administration of vasopressin in the absence or presence of other vasoactive medications often stabilizes hemodynamics and improves survival in patients with sepsis. The combined use of vasopressin with other vasoactive medications reduces the overall dose of vasopressin required to maintain arterial pressure, thereby limiting the adverse effects of vasopressin on organ perfusion. In fact, sustained administration of higher doses of vasopressin may produce mesenteric ischemia, peripheral vascular insufficiency, and cardiac arrest because the drug causes pronounced vasoconstriction of cutaneous, skeletal muscle, splanchnic, and coronary vascular beds, concomitant with reduced perfusion of and oxygen delivery to these tissues. Bolus intravenous administration of vasopressin is also used as part of the American Heart Association Adult Advanced Cardiac Life Support algorithm for cardiac arrest resulting from ventricular fibrillation, pulseless electrical activity, or asystole.

Nitrovasodilators

Organic nitrates (e.g., nitroglycerin) and nitric oxide (NO) donors (e.g., sodium nitroprusside) are nitrovasodilators that release NO through enzymatic sulfhydryl group reduction or through a spontaneous mechanism that occurs independent of metabolism, respectively. Like endogenous NO produced by vascular endothelium, exogenous NO stimulates guanylate cyclase within the vascular smooth muscle cell to convert guanosine triphosphate to cGMP. The second messenger activates a cGMP-dependent

protein kinase (protein kinase G) that dephosphorylates myosin light chains and contributes to relaxation of vascular smooth muscle. NO stimulates Ca^{2+} reuptake into the sarcoplasmic reticulum by activating the sarcoplasmic reticulum Ca^{2+} ATPase through a cGMP-independent mechanism. This action decreases intracellular Ca^{2+} concentration and causes relaxation. NO also stimulates K^+ efflux from the cell by activating the K^+ channel. This shift in K^+ balance produces cellular hyperpolarization, which, in turn, closes the voltage-gated Ca^{2+} channel and facilitates relaxation.

Nitrovasodilators are often used to improve hemodynamics and myocardial oxygen supply-demand relations in patients with heart failure. Venodilation reduces venous return, contributing to declines in LV and RV end-diastolic volume, pressure, and wall stress. Arterial vasodilation also reduces systemic and pulmonary arterial pressures, which decreases LV and RV end-systolic wall stress, respectively. These actions combine to decrease myocardial oxygen consumption. Simultaneously, nitrovasodilators increase myocardial oxygen supply through direct dilation of epicardial coronary arteries in the absence of flow-limiting stenoses. The reduction in LV end-diastolic pressure observed during administration of nitrovasodilators coupled with coronary vasodilation substantially enhances subendocardial perfusion. The clinical efficacy of nitrovasodilators may display some initial variability between patients, but the cardiovascular effects of these drugs inevitably diminish with prolonged use. Some patients may be relatively resistant to the effects of organic nitrates in the presence of oxidative stress because superoxide anions scavenge NO, cause reversible oxidation of guanylate cyclase, and inhibit aldehyde dehydrogenase. The latter action prevents the release of NO from organic nitrates. A progressive attenuation of hemodynamic responses to nitrovasodilators may develop in other patients as a result of sympathetic nervous system and renin-angiotensin-aldosterone axis activation. This phenomenon, termed “pseudotolerance,” accounts for the rebound hypertension that may be observed after abrupt discontinuation of nitrovasodilator therapy. Inhibition of guanylate cyclase activity is most likely responsible for true tolerance to organic nitrates. A daily “drug holiday” is a useful strategy for reversing this effect in patients requiring prolonged treatment. Administration of *N*-acetylcysteine, a sulfhydryl donor, may also be effective for reversing true tolerance. Notably, prolonged use of organic nitrates may also cause methemoglobinemia, interfere with platelet aggregation, and produce heparin resistance. It is important to recognize that organic nitrates should also be used with caution in patients receiving phosphodiesterase type V inhibitors (e.g., sildenafil) because NO-induced vasodilation is enhanced, and profound hypotension, myocardial ischemia or infarction, and death may result.

Nitroglycerin

Nitroglycerin dilates venules to a greater degree than arterioles. At lower doses, the organic nitrate produces venodilation without causing a significant decrease in systemic vascular resistance. Arterial pressure and cardiac output fall in response to the reduction in preload despite a modest baroreceptor reflex-mediated increase in heart rate. Nitroglycerin also decreases pulmonary arterial pressures and vascular resistance. At higher doses, nitroglycerin dilates arterioles and reduces LV afterload. These effects cause more pronounced decreases in arterial pressure and stimulate greater reflex tachycardia. Overshoot hypotension and tachycardia is particularly common in the setting of hypovolemia, such as is often observed in patients with poorly controlled essential hypertension and parturients with pregnancy-induced hypertension.

Nitroglycerin improves the balance of myocardial oxygen supply to demand through its actions as a direct coronary vasodilator (which increase supply) and its systemic hemodynamic effects (which reduce demand). Nitroglycerin dilates both normal and poststenotic epicardial coronary arteries, enhances blood flow through coronary collateral vessels, and preferentially improves subendocardial perfusion. The drug also inhibits coronary vasospasm and dilates arterial conduits (e.g., internal mammary artery, radial artery) used during CABG surgery. Nitroglycerin decreases myocardial oxygen demand by reducing LV preload, and to a lesser extent afterload, thereby producing corresponding reductions in LV end-diastolic and end-systolic wall stress. These effects are particularly important in patients with acutely decompensated heart failure resulting from myocardial ischemia. Thus, nitroglycerin is a very effective first-line drug for the treatment of myocardial ischemia. Nevertheless, caution should be exercised when using nitroglycerin in patients with ischemia who are also hypovolemic because the drug may precipitate life-threatening hypotension by further compromising coronary perfusion pressure and reducing coronary blood flow despite epicardial vasodilation. These actions may inadvertently worsen myocardial ischemia.

Sodium Nitroprusside

Sodium nitroprusside is an ultra-short-acting direct NO donor. It is a potent venous and arterial vasodilator that rapidly reduces arterial pressure by decreasing LV preload and afterload,

respectively. Not surprisingly, sodium nitroprusside is a firstline drug for the treatment of hypertensive emergencies. Sodium nitroprusside is also useful for the treatment of cardiogenic shock because arterial vasodilation improves forward flow by reducing impedance to LV ejection while venodilation decreases LV filling pressures. Unlike nitroglycerin, sodium nitroprusside is relatively contraindicated in patients with acute myocardial ischemia because the drug causes abnormal redistribution of coronary blood flow away from ischemic myocardium (“coronary steal”). This effect occurs because sodium nitroprusside produces greater coronary vasodilation in vessels that perfuse normal myocardium compared with those that supply the ischemic territory, the latter of which are already maximally vasodilated. Baroreceptor reflexmediated tachycardia is also more pronounced during administration of sodium nitroprusside compared with nitroglycerin because the direct NO donor is a more potent arteriolar vasodilator than the organic nitrate. This reflex tachycardia dramatically increases heart rate and myocardial oxygen consumption, thereby exacerbating acute myocardial ischemia. Sodium nitroprusside is often combined with a β_1-adrenoceptor antagonist such as esmolol to decrease arterial pressure, depress myocardial contractility, and reduce ascending aortic wall stress in patients with acute aortic dissection until direct surgical control of the injury can be achieved. Clinical use of sodium nitroprusside is limited by its toxic metabolites, which predictably accumulate when administration is prolonged or relatively high doses are used. Metabolism of sodium nitroprusside produces cyanide, which binds with cytochrome C to inhibit aerobic metabolism and cause lactic acidosis. Cyanide derived from sodium nitroprusside metabolism also binds with hemoglobin to form methemoglobin and with sulfur to form thiocyanate. The latter metabolite may accumulate in patients with renal insufficiency and produce neurologic complications including delirium and seizures.

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13.4 Nitroprusside

Hydralazine

Hydralazine is a direct vasodilator that reduces intracellular Ca^{2+} concentration in vascular smooth muscle. Activation of K_{ATP} channels is partially responsible for this effect, which results in direct relaxation of small arteries and arterioles in coronary, cerebral, splanchnic, and renal vascular beds, declines in systemic vascular resistance, and decreases in arterial pressure. LV preload is relatively preserved because hydralazine does not dilate venous capacitance vessels. The primary reduction in afterload stimulates baroreceptor reflex-mediated tachycardia and increases cardiac output. The magnitude of tachycardia observed with administration of hydralazine is often greater than expected based solely on baroreceptor reflexes alone and may reflect a direct effect of the drug on cardiovascular regulation in the central nervous system. This pronounced tachycardia might produce acute myocardial ischemia in patients with critical coronary stenoses based on increases in myocardial oxygen demand. Hydralazine-induced tachycardia responds appropriately to β_1-adrenoceptor antagonists, but caution should be exercised because further declines in arterial pressure may also occur.

Hydralazine is commonly used for management of sustained postoperative hypertension in the absence of tachycardia.

Calcium Channel Blockers

Ca^{2+} channels are asymmetric biochemical pores consisting of at least four subunits (α_1, α_2/δ, and β with or without gamma) that traverse many biologic membranes.[137] Ca^{2+}

channels are closed under quiescent conditions, but they may open through a voltage-dependent or receptor-operated mechanism to allow Ca^{2+} entry into the cell or an organelle (e.g., mitochondria, sarcoplasmic reticulum). Myocardial and vascular smooth muscle cell membranes contain two types of voltage-dependent Ca^{2+} channels that are defined on the basis of the duration of opening: T (transient) and L (long). The L-type Ca^{2+} channel is the predominant target of Ca^{2+} channel blockers in current clinical use. These drugs do not block the T-type Ca^{2+} channel. Ca^{2+} channel blockers may be divided into four chemical groups including 1,4-dihydropyridines (e.g., nifedipine, nicardipine, nimodipine, clevidipine), benzothiazepines (diltiazem), phenylalkylamines (verapamil), and diarylaminopropylamine ethers (bepridil), the first three of which are used clinically (Table 13-8).

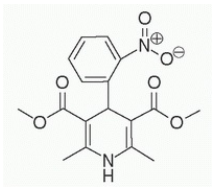
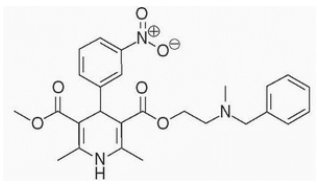
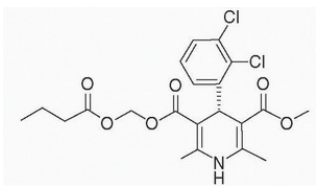
11 In general, Ca^{2+} channel blockers produce varying degrees of vasodilation; direct negative chronotropic, dromotropic, and inotropic effects; and baroreceptor reflex-mediated increases in heart rate, depending on each drug's selectivity for myocardial and vascular smooth muscle L-type Ca^{2+} channels. All Ca^{2+} channel blockers produce greater relaxation of arterial, compared with venous, vascular smooth muscle. As a result, LV afterload is reduced while preload is relatively preserved. Ca^{2+} channel blockers cause coronary arterial vasodilation and inhibit coronary artery vasospasm. These actions may enhance coronary blood flow assuming that coronary perfusion pressure is not substantially reduced as a result of arterial vasodilation. In addition to causing declines in LV afterload, some Ca^{2+} channel blockers (e.g., diltiazem, verapamil) also reduce myocardial oxygen consumption by decreasing heart rate and myocardial contractility. However, other Ca^{2+} channel blockers (e.g., dihydropyridines) may increase myocardial oxygen consumption because of baroreceptor reflex-induced tachycardia. As a result, these Ca^{2+} channel blockers may not exert anti-ischemic effects in patients with hemodynamically significant coronary artery stenoses.

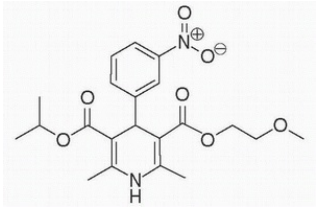
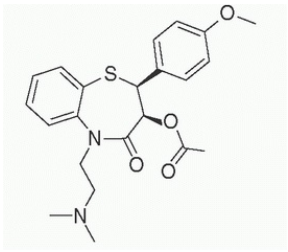
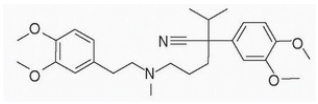
Nifedipine

Nifedipine and other related dihydropyridine Ca^{2+} channel blockers (e.g., amlodipine, felodipine, isradipine) are most often used for chronic treatment of essential hypertension. Like other Ca^{2+} channel blockers, nifedipine is a relatively selective arterial vasodilator that does not substantially affect venous vasomotor tone. This effect decreases arterial pressure, but in so doing, activates the sympathetic nervous system and elicits baroreceptor reflex-mediated increases in heart rate. Nifedipine produces direct myocardial depression in vitro, but this negative inotropic effect is not evident when the drug is used clinically because arterial vasodilation occurs at plasma concentrations that are substantially less than those required for reductions in myocardial contractility. Similarly, typical doses of nifedipine only minimally alter SA node automaticity and AV conduction. Maintenance of venous return and contractility state combined with modest tachycardia and a decline in LV afterload result in small increases in cardiac output. Nifedipine is frequently used in patients with coronary artery disease, most often in combination with a β_1-adrenoceptor antagonist to abolish baroreceptor reflex-mediated tachycardia,[138] because the Ca^{2+} channel blocker decreases myocardial oxygen consumption via a reduction in LV afterload and is a direct epicardial coronary vasodilator. Another more specific indication for this Ca^{2+} channel blocker is variant angina, a disease process in which reductions in coronary blood flow occur as a result of regional coronary vasoconstriction independent of coronary artery stenoses.[138] Nifedipine is probably more effective than nitrates for the treatment of variant

angina because the Ca^{2+} channel blocker causes more profound, consistent coronary vasodilation. Vasospasm may also occur in patients with unstable angina resulting from atherosclerosis, and nifedipine may also be beneficial in this setting.[139] Despite these salutary effects, nifedipine does not improve and may worsen mortality when used in patients with acute myocardial infarction, in contrast to other Ca^{2+} channel blockers such as diltiazem and verapamil.[140] Nifedipine is also used to provide arterial vasodilation in patients with Raynaud's phenomenon.[141]

Table 13-8 Comparative Effects of Ca^{2+} Channel Blockers

Name	Chemical Structure	Myocardial Depression	Coronary Blood Flow	Suppression of SA Node (Automaticity)	Suppression of AV Node (Conduction)
Nifedipine		+	+++++	+	0
Nicardipine		0	+++++	+	0
Clevidipine		+	+++++	+	0
Nimodipine		+	++++	+	0

					
Diltiazem		++	+++	+++++	++++
Verapamil		++++	++++	+++++	++++

SA, sinoatrial; AV, atrioventricular.

Adapted with permission from Michel T, Hoffman BB. Treatment of myocardial ischemia and hypertension. In: Brunton LL, Chabner BA, Knollman BC, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York, NY: McGraw-Hill Medical; 2011:756.

Nicardipine

Nicardipine is another dihydropyridine Ca^{2+} channel antagonist that is highly selective for vascular smooth muscle. Nicardipine produces cardiovascular effects that are similar to nifedipine, but has a longer half-life than the latter drug. Nicardipine is a profound vasodilator because of its pronounced inhibition of Ca^{2+} influx in vascular smooth muscle. Like other dihydropyridine Ca^{2+} channel antagonists, nicardipine preferentially dilates arteriolar vessels; this effect decreases arterial pressure. In contrast to diltiazem and verapamil, nicardipine does not substantially depress myocardial contractility nor does the drug affect the rate of SA node firing. As a result, stroke volume and cardiac output are relatively preserved or may increase. Nicardipineinduced decreases in arterial pressure trigger increases in heart rate through activation of baroreceptor reflexes, but the tachycardia observed during administration of nicardipine is less pronounced than typically occurs with sodium nitroprusside at comparable levels of arterial pressure. Nicardipine is also a highly potent coronary vasodilator and is often used to dilate arterial conduits during coronary artery bypass graft surgery. Because of its relatively long half-life, nicardipine is primarily used for treatment of sustained perioperative hypertension and not for acute, often transient hypertensive episodes that are commonly observed during surgery.

Clevidipine

Clevidipine is an ultra-short-acting dihydropyridine Ca^{2+} channel antagonist with a plasma half-life of approximately 2 minutes after intravenous administration.[142,143] Like nicardipine and nifedipine, clevidipine exerts pronounced effects at the less negative resting membrane potentials typically observed in vascular smooth muscle cells, but demonstrates lower potency in cardiac myocytes in which resting membrane potentials are substantially more negative. As a result of these differences in cellular electrophysiology, clevidipine is highly selective for arterial vascular smooth muscle and is nearly devoid of negative chronotropic or inotropic effects. This hemodynamic profile may be especially useful for the treatment of hypertension in patients with compromised LV function in the absence or presence of acute heart failure.[144] Clevidipine causes dose-related arteriolar vasodilation while sparing venous vasomotor tone, thereby reducing systemic vascular resistance and arterial pressure without affecting LV preload. These actions may combine to augment cardiac output. Modest increases in heart rate may also occur during administration of clevidipine as a result of baroreceptor reflex activation. Unlike other short-acting antihypertensive drugs, clevidipine is not associated with the development of tachyphylaxis, and abrupt discontinuation of the drug does not appear to cause rebound hypertension. Because tissue and plasma esterases are responsible for clevidipine metabolism, little to no accumulation of the drug occurs even in the setting of hepatic or kidney dysfunction. Clevidipine compares favorably with nitroglycerin, sodium nitroprusside, and nicardipine for the treatment of acute hypertension in cardiac surgery patients.[145] Clevidipine has also demonstrated efficacy for treatment of hypertension associated with pheochromocytoma[146] and acute intracerebral hemorrhage.[147] The short-acting Ca^{2+} channel blocker is also useful for producing controlled hypotension during spinal surgery.[148]

Nimodipine

The dihydropyridine nimodipine is more lipophilic and more easily crosses the blood-brain barrier than other drugs in this class of Ca^{2+} channel blockers. As a result, nimodipine exerts more cerebral arterial vasodilation than other dihydropyridines. Nimodipine is currently the only medication approved by the U.S. Food and Drug Administration for treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage.[149,150] Several clinical trials demonstrated that nimodipine significantly reduces the severity of symptoms resulting from cerebral vasospasm, the incidence of cerebral infarction, the occurrence of delayed neurologic deficits, and the risk of mortality while improving long-term neurologic functional status after the initial hemorrhage.[151,152] Nimodipine does not affect the incidence of recurrent hemorrhage or prevent other adverse reactions.[152] Nimodipine also does not reverse angiographic evidence of vasospasm, indicating that the mechanism by which the Ca^{2+} channel blocker improves outcome in this setting is most likely not related to dilation of large cerebral arteries. Instead, nimodipine appears to reduce cerebral arteriolar resistance and enhance blood flow through pia mater collateral vessels. In addition, nimodipine may attenuate Ca^{2+}-mediated neurotoxicity and thereby exert clinically beneficial neuroprotective effects.[153]

Diltiazem

Diltiazem is the only benzothiazepine Ca^{2+} channel blocker in current clinical use.[154] The cardiovascular effects of diltiazem are somewhat different from those produced by the dihydropyridines. Intravenous administration of diltiazem produces arterial vasodilation and decreases arterial pressure. These actions initially stimulate baroreceptor reflex-mediated tachycardia and increase cardiac output, but heart rate subsequently falls because, in contrast to dihydropyridine Ca^{2+} channel blockers, diltiazem exerts potent negative chronotropic and dromotropic effects on SA node automaticity and AV node conduction, respectively. Oral administration of diltiazem reduces heart rate,

arterial pressure, and myocardial oxygen consumption. Both routes of administration cause coronary vasodilation and moderate negative inotropic effects. These combined properties make diltiazem a useful alternative medication for the treatment of patients with hypertension and symptomatic coronary artery disease[155] in clinical situations in which β-adrenoceptor antagonists may be relatively contraindicated (e.g., asthma, chronic obstructive pulmonary disease). Similarly, diltiazem may also prevent subsequent myocardial infarction in patients who have already suffered an infarction but cannot receive a β-adrenoceptor antagonist.[138] Because diltiazem prolongs AV node conduction, the drug may be effective for ventricular rate control in patients with chronic atrial fibrillation, atrial flutter, or supraventricular tachycardia.[156],[157] However, adenosine or cardioversion (depending on the magnitude of accompanying hypotension) remains the recommended treatment for symptomatic supraventricular tachycardia in the 2015

American Heart Association Advanced Adult Cardiovascular Life Support guidelines.[158]

Verapamil

The phenylalkylamine Ca^{2+} channel blocker verapamil produces less arterial vasodilation, but exerts more potent effects on automaticity, conduction, and myocardial contractility than the dihydropyridines. As a result, baroreceptor reflex-mediated increases in heart rate that may be expected because of reductions in arterial vasomotor tone and systemic vascular resistance do not occur. The sympathetic nervous system activation resulting from arterial vasodilation generally compensates for the direct negative inotropic effect of verapamil, and cardiac output is maintained or modestly increased because of the decline in LV afterload in patients with normal LV function. However, verapamil has the potential to markedly worsen pre-existing LV systolic dysfunction in patients with heart failure because of the Ca^{2+} channel blocker's myocardial depressant effects. Like diltiazem, verapamil is a coronary vasodilator and decreases myocardial oxygen consumption as a result of its hemodynamic effects. Thus, verapamil may be effective for the treatment of angina pectoris and myocardial infarction in patients who may be unable to tolerate β_1-adrenoceptor antagonists.[159]

The actions of verapamil on cardiac electrophysiology make the Ca^{2+} channel antagonist a useful alternative to adenosine for the treatment of supraventricular tachyarrhythmias.[158] Reentry through the SA node or AV node is responsible for the vast majority of supraventricular tachyarrhythmias except when an aberrant conduction ("pre-excitation") pathway is present (e.g., the bundle of Kent in Wolff-Parkinson-White syndrome).[160] Similar to but to a greater extent than diltiazem, verapamil reduces the rate of SA node discharge, markedly decreases AV node conduction velocity, and increases the refractory period of the AV node consistent with a class IV antiarrhythmic. These actions predictably prolong PR interval and increase AV conduction time. For example, verapamil has been shown to significantly reduce the risk of supraventricular tachyarrhythmias in patients undergoing cardiac and noncardiac surgery because of these actions on the proximal cardiac conduction system.[161],[162] Verapamil may also be useful for the treatment of atrial fibrillation or flutter with rapid ventricular response because the drug substantially reduces ventricular rate and may occasionally facilitate conversion of the atrial arrhythmia to sinus rhythm. Verapamil is contraindicated in the presence of an aberrant re-entry supraventricular tachyarrhythmia because blockade of AV conduction leaves direct transmission from the atrium to the ventricle through the aberrant pathway unopposed, thereby exposing the patient to the risk of malignant ventricular arrhythmias and sudden cardiac death.[163] Administration of verapamil in the presence of a β_1-adrenoceptor antagonist may cause complete heart block or profound myocardial depression. Verapamil is also contraindicated in patients with sick sinus syndrome or atrioventricular node dysfunction.[164]

Angiotensin-converting Enzyme Inhibitors

The renin-angiotensin-aldosterone system is another major regulator of cardiovascular homeostasis. Renal cortical juxtaglomerular cells secrete renin in response to decreases in Na^+ reabsorption by the macula densa, reduced perfusion pressure to preglomerular arterioles, and β_1-adrenoceptor stimulation resulting from sympathetic nervous system activation. Renin cleaves angiotensinogen into the 10 amino acid peptide angiotensin I (Fig. 13-7). Angiotensin-converting enzyme (synthesized in pulmonary vascular endothelium) then excises the C-terminal histidine and leucine residues from the angiotensin I molecule to form the biologically active octapeptide angiotensin II. A potent vasoconstrictor of renal and mesenteric arterioles through its actions at the angiotensin subtype I (AT_1) receptor mediated through G_q protein-phospholipase C-inositol triphosphate-Ca^{2+} signaling,[165] angiotensin II also facilitates the release of norepinephrine from sympathetic postganglionic neurons and augments the actions of the endogenous catecholamine in vascular smooth muscle. In addition, angiotensin II enhances release of norepinephrine and epinephrine from the adrenal medulla and attenuates baroreceptor-mediated reductions in sympathetic nervous system tone that occur in response to compensatory elevations in arterial pressure. Angiotensin II inhibits renal tubular reabsorption of Na^+, thereby reducing Na^+ and water excretion and enhancing K^+ excretion. Angiotensin II further stimulates the synthesis and release of aldosterone from the zona glomerulosa of the adrenal cortex. Aldosterone augments the actions of angiotensin II on renal tubular Na^+ retention and K^+ excretion. The net result of these collective effects is elevated arterial pressure and increased intravascular volume.

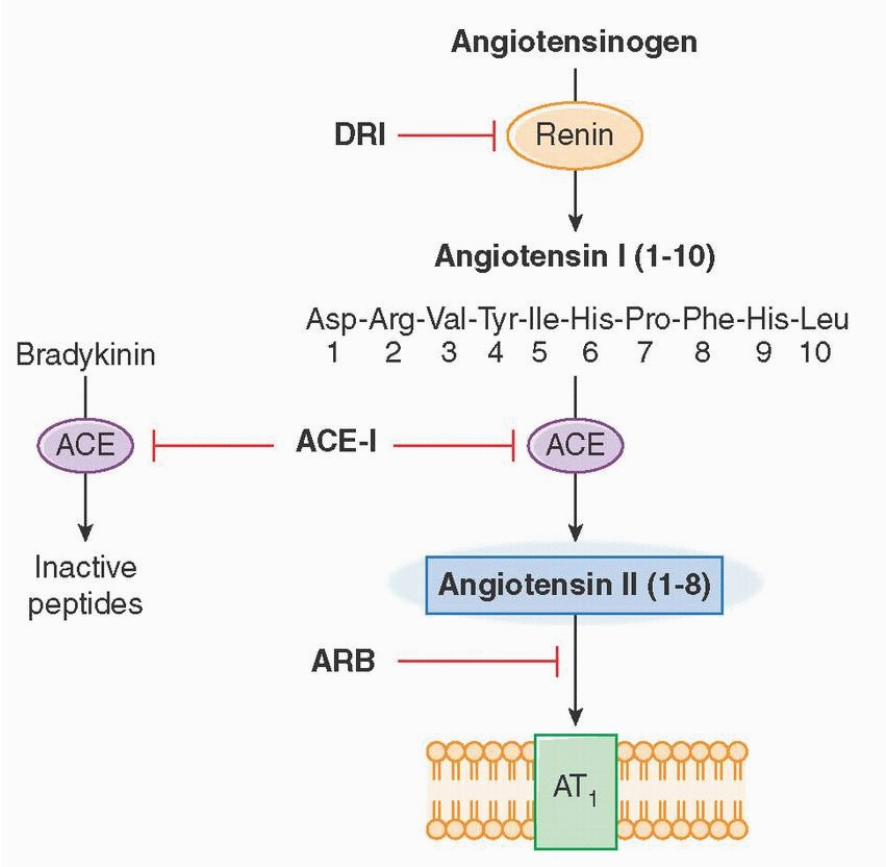


Figure 13-7 Schematic illustration of inhibitors of the reninangiotensin system; abbreviations: DRI, direct renin inhibitor; ACE, angiotensin-converting enzyme; ACE I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AT_1, angiotensin subtype 1 receptor. (Adapted with permission from Hilal-Dandan R. Renin and angiotensin. In: Brunton LL, Chabner BA, Knollman BC, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York, NY: McGraw-Hill Medical; 2011:731.)

ACE inhibitors block the conversion of angiotensin I to angiotensin II. As may be predicted based on the aforementioned effects of angiotensin II, ACE inhibitors are potent antihypertensive medications. There are currently eleven ACE inhibitors in clinical use in the United States, which differ in potency, duration of action, metabolism and clearance, and whether hepatic esterase conversion of a prodrug form to a metabolite is required for activity (e.g., enalapril, quinapril, ramipril). Captopril was the first ACE inhibitor, but its use has diminished to some extent because the drug is associated with a greater number of adverse

side effects and possible drug interactions than other ACE inhibitors. Enalapril is the only ACE inhibitor available in an intravenous form (enalaprilat), whereas lisinopril is the only orally administered drug in this class with a prolonged half-life that does not require multiple daily dosing. ACE inhibitors reduce LV afterload and decrease arterial pressure through a reduction in arterial vasomotor tone in patients with essential or renal vascular hypertension, but not in those with primary aldosteronism. Cardiac output remains unchanged or modestly increases while LV preload is unaffected. Sympathetic nervous system tone does not change despite the decrease in arterial pressure, and baroreceptormediated reflexes remain intact. As a result, patients do not develop orthostatic hypotension or limited exercise capacity when treated with an ACE inhibitor unless relative hypovolemia is present because of concomitant diuretic therapy; the ACE inhibitor is administered with another arterial vasodilator (e.g., Ca^{2+} channel blocker); or elevated plasma renin concentrations are present.

ACE inhibitors have been shown to be very effective in the treatment of LV systolic dysfunction with or without heart failure. Several large-scale, randomized, controlled double blind clinical trials provided convincing evidence that ACE inhibitors halt or delay the progression of heart failure and improve quality of life in patients resulting from LV systolic or diastolic dysfunction. ACE inhibitors also cause declines in the need for hospitalization, the incidence of myocardial infarction, and the risk of sudden cardiac death. In the presence of LV dysfunction, ACE inhibitors decrease LV afterload, improve arterial compliance, reduce arterial pressure, enhance cardiac output, increase renal blood flow, and facilitate natriuresis. The hemodynamic effects serve to reduce chronically elevated sympathetic nervous system tone because tissue perfusion improves, whereas the renal actions result in beneficial reductions in intravascular volume. ACE inhibitors have well-documented salutary effects in patients with acute myocardial infarction, especially those with diabetes mellitus and hypertension.[166] ACE inhibitors also substantially reduced the incidence of myocardial infarction, cerebrovascular accident, and mortality in patients at high risk for major adverse cardiovascular events.[167] Finally, ACE inhibitors exert renal protective effects in diabetic patients and mitigate the progression of renal dysfunction in other forms of nephropathy as well.[168]

ACE inhibitors produce several side effects, the most common of which is a dry cough that affects as many as 20% of patients treated with these medications. Blockade of ACE-induced degradation of bradykinin exacerbates the pulmonary effects of the inflammatory mediator and contributes to this clinical problem. Nonsteroidal anti-inflammatory drugs attenuate the ability of ACE inhibitors to reduce arterial pressure in patients with hypertension. ACE inhibitors may also cause hyperkalemia in patients with chronic kidney injury and in those with normal renal function who are treated with K^+-sparing diuretics (e.g., spironolactone, triamterene) or K^+ supplements. Conversely, ACE inhibitors blunt the hypokalemic effects of thiazide and loop diuretics. Acute renal failure, reversible neutropenia, fetal teratogenicity, and dermatitis are other adverse effects of ACE inhibitors. Angioedema is a potentially life-threatening, although rare (0.1% to 0.5% of patients), complication of ACE inhibitors in which rapidly developing edema of the lips, nose, tongue, mouth, hypopharynx, and glottis occurs that may quickly jeopardize airway integrity.[169] Angioedema resulting from an ACE inhibitor usually occurs with the initial dose of the drug and may require emergent endotracheal intubation or a surgical airway to prevent death from asphyxia. Notably, African-Americans are approximately 4.5-fold more likely to develop this complication than are their Caucasian counterparts.[170] Perhaps of most relevance to the anesthesiologist, chronic treatment with an ACE inhibitor may precipitate profound hypotension in the presence of vasodilating general anesthetics that is refractory to treatment with phenylephrine, ephedrine, or norepinephrine.[171],[172] Vasopressinergic V_1 agonists (e.g., terlipressin) are more effective than norepinephrine in treating this form of intraoperative hypotension.[173],[174] Discontinuation of ACE inhibitor therapy before elective surgery is recommended to avoid this complication.

Angiotensin Receptor Blockers

12 Angiotensin receptor blockers inhibit the AT_1 receptor with high affinity and thereby markedly attenuate the cardiovascular, endocrine, and renal effects of angiotensin II.[175] All ARBs are potent antihypertensive medications that more effectively inhibit the actions of angiotensin II at AT_1 receptors than do ACE inhibitors. In contrast to ACE inhibitors, ARBs do not affect angiotensin II-induced activation of angiotensin subtype 2 (AT_2) receptors. The clinical implications of these differences in pharmacodynamics between ARBs and ACE inhibitors remain unclear. ARBs and ACE inhibitors reduce arterial pressure to equivalent degrees, but angiotensin receptor blockers produce fewer side effects. Similar to ACE inhibitors, ARBs (e.g., losartan, candesartan, valsartan) improved functional capacity and reduced morbidity and mortality in patients with heart failure[176] and acute myocardial infarction complicated by LV dysfunction.[177] Whether the combination of an ARB and an ACE inhibitor provides any added clinical benefits in these settings has not been resolved.[178] ARBs are most often used in patients with heart failure who are unable to tolerate the side effects of ACE inhibitors, the latter of which continue to be used as first-line medications in heart failure pharmacotherapy. Like ACE inhibitors, ARBs provide renal protection in patients with diabetes mellitus independent of the effects of these drugs on arterial pressure.[179] ARBs also reduce the risk of stroke in patients with hypertension, maintain sinus rhythm after cardioversion in patients with long-term atrial fibrillation, and improve symptoms in patients with hepatic cirrhosis-induced portal hypertension. As predicted by their pharmacologic mechanism of action, ARBs are less likely to cause cough, dermatitis, or angioedema than ACE inhibitors. However, angiotensin receptor blockers exert fetal toxicity and may cause hyperkalemia in patients treated with K^+-sparing diuretics or those with renal insufficiency similar to ACE inhibitors.

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