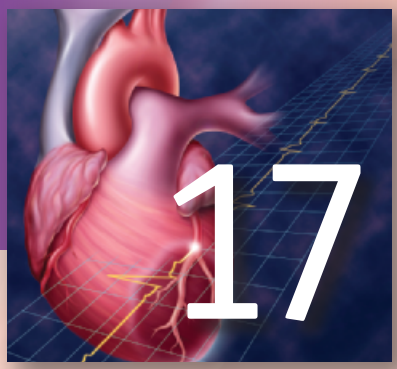

17 Cardiovascular Drugs

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Chapter Outline

This chapter reviews the physiologic basis and clinical use of cardiovascular drugs. Although a multitude of drugs are available to treat cardiac disorders, these agents can be grouped by their pharmacologic actions into a small number of categories. Additionally, many drugs are useful in more than one form of heart disease.

INOTROPIC DRUGS AND VASOPRESSORS

Inotropic drugs are used to increase the force of ventricular contraction when myocardial systolic function is impaired. The pharmacologic agents in this category include the cardiac glycosides, sympathomimetic amines, and phosphodiesterase-3 inhibitors (Table 17-1). Although they work through different mechanisms, they are all thought to enhance

TABLE 17-1 Inotropic Drugs

Class	Examples
Cardiac glycosides	Digoxin
Sympathomimetic amines	Dopamine
	Dobutamine
	Norepinephrine
	Epinephrine
	Isoproterenol
Phosphodiesterase-3 inhibitors	Milrinone

cardiac contraction by increasing the intracellular calcium concentration, thus augmenting actin and myosin interaction. The hemodynamic effect is to shift a depressed ventricular performance curve (Frank-Starling curve) in an upward direction (Fig. 17-1), so that for a given ventricular filling pressure, stroke volume and cardiac output (CO) are increased.

Cardiac Glycosides (Digitalis)

The cardiac glycosides are called "digitalis" because the drugs of this class are based on extracts of the foxglove plant, *Digitalis purpurea*. The most commonly used member of this group is **digoxin**.

Mechanism of Action

The two desired effects of digoxin are (1) to improve contractility of the failing heart (mechanical effect) and (2) to prolong the refractory period of the atrioventricular (AV) node in patients with supraventricular arrhythmias (electrical effect).

Mechanical Effect

The action by which digoxin improves contractility is attributed to inhibition of sarcolemmal Na^+K^+-ATPase, which is normally responsible for maintaining transmembrane Na^+ and K^+ gradients. By inhibiting this transporter, digitalis causes the intracellular $[Na^+]$ to rise. As

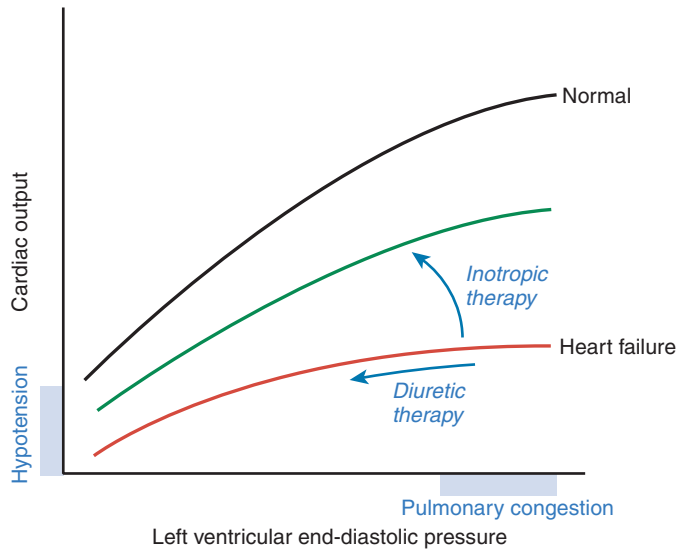

Figure 17-1. Ventricular performance (Frank-Starling) curve. In systolic heart failure, the curve is displaced downward, so that at a given left ventricular end-diastolic pressure (LVEDP), the cardiac output is lower than in a normal heart. Diuretics reduce LVEDP but do not change the position of the curve; thus, pulmonary congestion improves but cardiac output may fall. Inotropic drugs shift the curve upward, toward normal, so that at any LVEDP, the cardiac output is greater.

shown in Figure 17-2, an increase in intracellular sodium content reduces Ca^{++} extrusion from the cell via the Na^+/Ca^{++} exchanger. Consequently, more Ca^{++} is pumped into the sarcoplasmic reticulum, and when subsequent action potentials excite the cell, a greater-than-normal amount of Ca^{++} is released to the myofilaments, thereby enhancing the force of contraction.

Electrical Effect

The major therapeutic electrical effect of digoxin occurs at the AV node, where it slows conduction and increases refractoriness by modulation of autonomic nervous system output (Table 17-2). Digoxin enhances vagal tone and reduces sympathetic activity, thus decreasing the frequency of transmission of atrial impulses through the AV node.

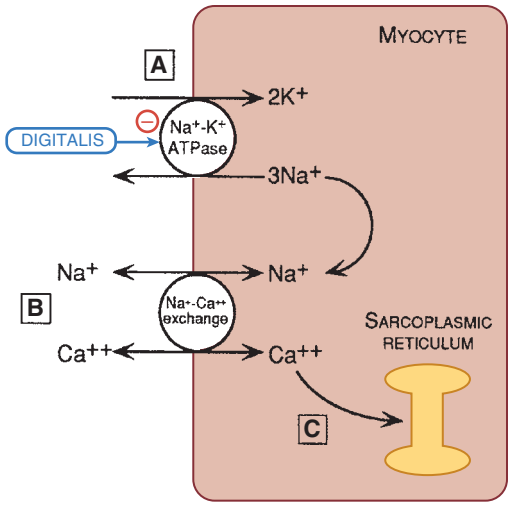

Figure 17-2. Mechanism of action of digitalis (inotropic effect). A. Digitalis inhibits the sarcolemmal Na^+K^+-ATPase, causing intracellular $[Na^+]$ to rise. **B.** Increased cytosolic $[Na^+]$ reduces the transmembrane Na^+ gradient; thus, the Na^+/Ca^+ exchanger drives less Ca^{++} out of the cell. **C.** The increased intracellular $[Ca^{++}]$ is stored in the sarcoplasmic reticulum, such that with subsequent action potentials, greater-than-normal Ca^{++} is released to the contractile elements in the cytoplasm, intensifying the force of contraction.

Clinical Uses

Digoxin has been used historically as an inotropic agent to treat heart failure with reduced ejection fraction (see Chapter 9). Although no longer a mainstay of therapy in heart failure, digitalis is sometimes useful in treating patients with heart failure complicated by atrial fibrillation. Unlike ACE inhibitors, β-blockers, and mineralocorticoid receptor antagonists, digoxin does not prolong the life expectancy of patients with chronic heart failure. Thus, its use has declined in recent years.

Digoxin is also occasionally prescribed as an antiarrhythmic agent, although other agents are more effective, safer, and used more frequently. By impairing AV nodal conduction, digitalis reduces the rate of ventricular stimulation in patients with rapid atrial fibrillation or atrial flutter. Digitalis may also terminate supraventricular reentrant tachycardias (eg, AVNRT—see Chapter 12), likely through enhancement of vagal tone, which slows impulse conduction and prolongs the effective refractory period of the AV node.

Pharmacokinetics and Toxicity

Digoxin is administered orally or intravenously and is excreted by the kidney. A series of loading doses is necessary to raise the drug's concentration into the therapeutic range. The subsequent maintenance dosage depends on the patient's renal function.

The potential for digitalis toxicity is significant because of a narrow therapeutic window. Many factors contribute to digitalis intoxication, the most common of which is hypokalemia, often caused by concurrent administration of diuretics. Hypokalemia exacerbates digitalis toxicity because it further inhibits Na^+K^+-ATPase. Other conditions that promote digitalis toxicity include hypomagnesemia and hypercalcemia. In addition, the administration of other drugs (eg, amiodarone) may raise the serum digoxin concentration by altering its clearance or volume of distribution.

Extracardiac signs of acute digitalis toxicity are often gastrointestinal (eg, nausea, vomiting, anorexia). Cardiac toxicity includes several types of arrhythmias, some of which may be life threatening (Table 17-2). In atrial tissue and ventricular Purkinje fibers, a high digoxin concentration results in three consequences that may lead to dangerous arrhythmias (Fig. 17-3):

TABLE 17-2 Electrophysiologic Effects of Digitalis

Region	Mechanism of Action	Clinical Effect
Therapeutic effects		
AV node	Vagal effect ↓ Conduction velocity ↑ Effective refractory period	↓ Rate of transmission of atrial impulses to the ventricles in supraventricular tachyarrhythmias
		May interrupt reentrant circuits passing through the AV node
Toxic effects		
Sinoatrial node	↑ Vagal effect and direct suppression	Sinus bradycardia
		Sinoatrial block (impulse not transmitted from SA node to atrium)
Atrium	Delayed afterdepolarizations (triggered activity), ↑ slope of phase 4 depolarization (↑ automaticity)	Atrial premature beats
		Nonreentrant SVT (ectopic rhythm)
	Variable effects on conduction velocity and ↑ refractory period (can fragment conduction and lead to re-entry)	Reentrant PSVT
AV node	Direct and vagal-mediated conduction block	AV block (first, second, or third degree)
AV junction (between AV node and His bundle)	Delayed afterdepolarizations (triggered activity), ↑ slope of phase 4 depolarization (↑ automaticity)	Accelerated junctional rhythm
Purkinje fibers and ventricular muscle	Delayed afterdepolarizations (triggered activity), ↓ conduction velocity and ↑ refractory period (can lead to reentry)	Ventricular premature beats
	↑ Slope of phase 4 depolarization (↑ automaticity)	Ventricular tachycardia

AV, atrioventricular; PSVT, paroxysmal supraventricular tachycardia; SA, sinoatrial; SVT, supraventricular tachycardia.

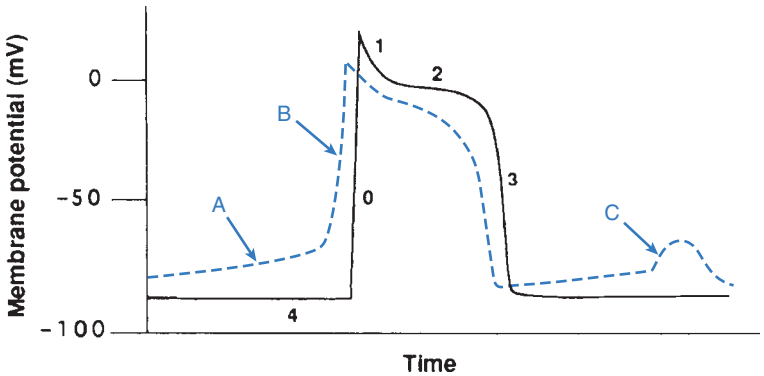

Figure 17-3. Direct effects of digitalis on the Purkinje cell action potential. The *solid tracing* represents depolarization and repolarization of a normal cell; the *dashed tracing* demonstrates the effects of digitalis. **A.** The maximum diastolic potential is less negative, and there is an increase in the slope of phase 4 depolarization, endowing the cell with intrinsic automaticity, and the potential for ectopic rhythms. **B.** Because depolarization of the cell occurs at a more positive voltage, there is partial inactivation of fast sodium channels, the rate of rise of phase 0 is decreased, and conduction velocity is slowed, which, if present heterogeneously among neighboring cells, produces conditions for reentry. **C.** Delayed afterdepolarizations may develop at high concentrations of digitalis in association with the increased intracellular calcium concentration and can result in triggered tachyarrhythmias.

1. *Less negative resting potential*. Inhibition of Na^+K^+-ATPase causes the resting potential to become less negative. Consequently, there is a voltage-dependent partial inactivation of the fast Na^+ channels, which leads to a slower rise of phase 0 depolarization and a reduction in conduction velocity (Fig. 1-16). The slowed conduction, if present heterogeneously among neighboring cells, enhances the possibility of reentrant arrhythmias.
2. *Decreased action potential duration*. Digitalis-induced elevated intracellular $[Ca^{++}]$ increases the activity of a Ca^{++}-dependent K^+ channel. The opening of this channel promotes K^+ efflux and more rapid *repolarization*. In addition, high intracellular $[Ca^{++}]$ inactivates Ca^{++} channels, decreasing the inward *depolarizing* Ca^{++} current. These effects decrease the action potential duration and shorten the refractory period, increasing the time during which cardiac fibers are responsive to external stimulation and allowing greater opportunity for propagation of arrhythmic impulses.
3. *Enhanced automaticity*. Digoxin enhances automaticity and may generate ectopic rhythms by two mechanisms:
   a. The less negative membrane resting potential can induce phase 4 gradual depolarization, even in nonpacemaker cells (see Chapter 11), and an action potential is triggered each time that threshold voltage is reached.
   b. The digoxin-induced increase in intracellular $[Ca^{++}]$ may trigger delayed afterdepolarizations (Fig. 17-3 and Chapter 11). If an afterdepolarization reaches the threshold voltage, an action potential (ectopic beat) is generated. Ectopic beats may lead to additional afterdepolarizations and self-sustaining arrhythmias such as ventricular tachycardia.

In addition, the augmented direct and indirect vagal effects of toxic doses of digitalis slow conduction through the AV node, such that various degrees of AV block, including complete heart block, can occur.

The treatment of digitalis-induced tachyarrhythmias may include administration of potassium (if hypokalemia is present), intravenous atropine for bradyarrhythmias, or lidocaine (discussed later in the chapter) for ventricular ectopy. High-grade AV block may require temporary pacemaker therapy. In patients with severe intoxication, administration of digoxin-specific antibodies may be lifesaving.

Sympathomimetic Amines

Sympathomimetic amines are inotropic drugs that bind to cardiac β_1-receptors leading to increased activity of adenylate cyclase and increased formation of cyclic adenosine monophosphate (cAMP) (Fig. 17-4). Increased cAMP activates specific protein kinases, which promote intracellular calcium influx by phosphorylating L-type calcium channels. The increased calcium entry triggers a corresponding rise in Ca^{++} release from the sarcoplasmic reticulum, which enhances the force of contraction. Intravenous dopamine and dobutamine are commonly used sympathomimetic amines in the treatment of acute heart failure. Table 17-3 summarizes the receptor actions and major hemodynamic effects of these agents.

Dopamine is an endogenous catecholamine and the precursor of norepinephrine. It possesses a combination of actions that makes it attractive in the treatment of heart failure associated with hypotension and poor renal perfusion. There are various types of receptors with different affinities for dopamine. At *low dosages*, <2 μg/kg/min, dopamine interacts primarily with dopaminergic receptors distributed in the renal and mesenteric vascular beds. Stimulation of these receptors causes local vasodilation and increases renal blood flow and glomerular filtration, facilitating diuresis.

Intermediate dosages of dopamine, 2-10 μg/kg/min, increase inotropy directly by stimulating cardiac β_1-receptors and indirectly by promoting norepinephrine release from sympathetic nerve terminals. These actions increase heart rate, cardiac contractility, and stroke volume, all of which augment CO.

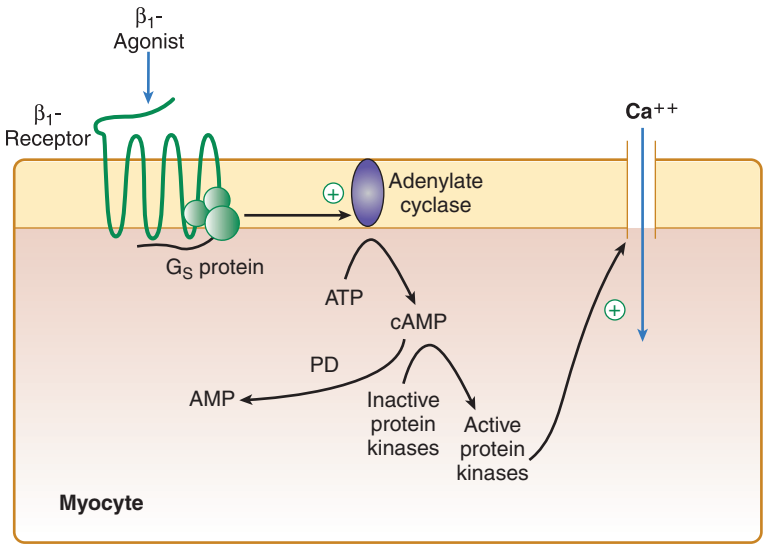

Figure 17-4. Mechanism by which β-adrenergic stimulation increases contractility. β_1-Receptor stimulation acts through G proteins (guanine nucleotide regulatory proteins), the alpha subunit (α) of which activates adenylate cyclase. The latter increases cyclic adenosine monophosphate (cAMP) production, which mediates protein kinase phosphorylation of cellular proteins, including ion channels. Phosphorylation of the slow Ca^{++} channel increases calcium influx, which augments the force of contraction. cAMP is degraded by phosphodiesterase (PD). ATP, adenosine triphosphate.

At *high dosages*, >10 μg/kg/min, dopamine also stimulates systemic α-receptors, thereby causing vasoconstriction and elevating systemic resistance. High-dose dopamine is indicated in hypotensive states such as shock. However, these doses are inappropriate in most patients with cardiac failure because the peripheral vasoconstriction increases the resistance against which the heart contracts (ie, higher afterload), which could impair left ventricular output.

The most important side effect of dopamine is provocation of tachyarrhythmias.

Dobutamine is a synthetic analog of dopamine that stimulates β_1-, β_2-, and α-receptors. It increases cardiac contractility by virtue of the β_1 effect but does not increase peripheral resistance because of the balance between α-mediated vasoconstriction and β_2-mediated vasodilation. Thus, it is useful in the treatment of heart failure not accompanied by hypotension. Unlike dopamine, dobutamine does not stimulate dopaminergic receptors (ie, no renal vasodilating effect), nor does it facilitate the release of norepinephrine from peripheral nerve endings. Like dopamine, it is useful for short-term therapy (<1 week), after which time it loses its efficacy, presumably because of down-regulation of adrenergic receptors. The major adverse effect is the provocation of tachyarrhythmias.

Norepinephrine is an endogenous catecholamine synthesized from dopamine in adrenergic postganglionic nerves and in adrenal medullary cells (where it is both secreted and serves as

TABLE 17-3 Sympathomimetic Drug Effects

	Receptor Stimulation			
Drug	**D_1 (↑ Renal Perfusion)**	**α (Vasoconstriction)**	**β_1 (↑ Contractility)**	**β_2 (Vasodilation)**
Dopamine	+[a]	++++[b]	++++	++
Dobutamine	0	+	++++	+
Norepinephrine	0	++++	++++	0
Epinephrine	0	++++[b]	++++	++
Isoproterenol	0	0	++++	++++

[a]Low dosage.
[b]High dosage.