Chapter 8

Cardiovascular Pharmacology

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ANTI-ISCHEMIC DRUG THERAPY

Anti-ischemic drug therapy during anesthesia is indicated whenever evidence of myocardial ischemia exists. The treatment of ischemia during anesthesia is complicated by the ongoing stress of surgery, blood loss, concurrent organ ischemia, and the patient's inability to interact with the anesthesiologist. Nonetheless, the fundamental principles of treatment remain the same as in the unanesthetized state. All events of myocardial ischemia involve an alteration in the oxygen supply/demand balance (Table 8-1). The 2007 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines on the Management and Treatment of Patients with Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction provide an excellent framework for the treatment of patients with ongoing myocardial ischemia.[1]

Nitroglycerin

Nitroglycerin (NTG) is clinically indicated as initial therapy in nearly all types of myocardial ischemia. Chronic exertional angina, de novo angina, unstable angina, Prinzmetal's angina (vasospasm), and silent ischemia respond to NTG

Table 8-1 Myocardial Ischemia: Factors Governing O_2 Supply and Demand

O_2 Supply	O_2 Demand
Heart rate*	Heart rate*
O_2 content	Contractility
Hemoglobin, percent oxygen saturation, Pao_2	Wall tension
Coronary blood flow	Afterload
CPP = DBP – LVEDP*	Preload (LVEDP)*
Coronary vascular resistance	

CPP = coronary perfusion pressure; DBP = diastolic blood pressure; LVEDP = left ventricular end-diastolic pressure.
*Affects both supply and demand.
Modified from Royster RL: Intraoperative administration of inotropes in cardiac surgery patients. J Cardiothorac Anesth 6(Suppl 5):17, 1990.

administration. During intravenous therapy with NTG, if blood pressure (BP) drops and ischemia is not relieved, the addition of phenylephrine will allow coronary perfusion pressure (CPP) to be maintained while allowing higher doses of NTG to be used for ischemia relief. If reflex increases in heart rate (HR) and contractility occur, combination therapy with β-adrenergic blockers may be indicated to blunt this undesired increase in HR. Combination therapy with nitrates and calcium channel blockers may be an effective anti-ischemic regimen in selected patients; however, excessive hypotension and reflex tachycardia may be a problem, especially when a dihydropyridine calcium antagonist is used.

Mechanism of Action

NTG enhances myocardial oxygen delivery and reduces myocardial oxygen demand. NTG is a smooth muscle relaxant that causes vasculature dilation.[2] Nitrate-mediated vasodilation occurs with or without intact vascular endothelium. Nitrites, organic nitrites, nitroso compounds, and other nitrogen oxide–containing substances (e.g., nitroprusside) enter the smooth muscle cell and are converted to reactive nitric oxide (NO) or *S*-nitrosothiols, which stimulate guanylate cyclase metabolism to produce cyclic guanosine monophosphate (cGMP) (Fig. 8-1). A cGMP-dependent protein kinase is stimulated with resultant protein phosphorylation in the smooth muscle. This leads to a dephosphorylation of the myosin light chain and smooth muscle relaxation. Vasodilation is also associated with a reduction of intracellular calcium. Sulfhydryl (SH) groups are required for formation of NO and the stimulation of guanylate cyclase. When excessive amounts of SH groups are metabolized by prolonged exposure to NTG, vascular tolerance occurs. The addition of *N*-acetylcysteine, an SH donor, reverses NTG tolerance. The mechanism by which NTG compounds are uniquely better venodilators, especially at lower serum concentrations, is unknown but may be related to increased uptake of NTG by veins compared with arteries.[3]

Physiologic Effects

Two important physiologic effects of NTG are systemic and regional venous dilation. Venodilation can markedly reduce venous pressure, venous return to the heart, and cardiac filling pressures. Prominent venodilation occurs at lower doses and does not increase further as the NTG dose increases. Venodilation results primarily in pooling

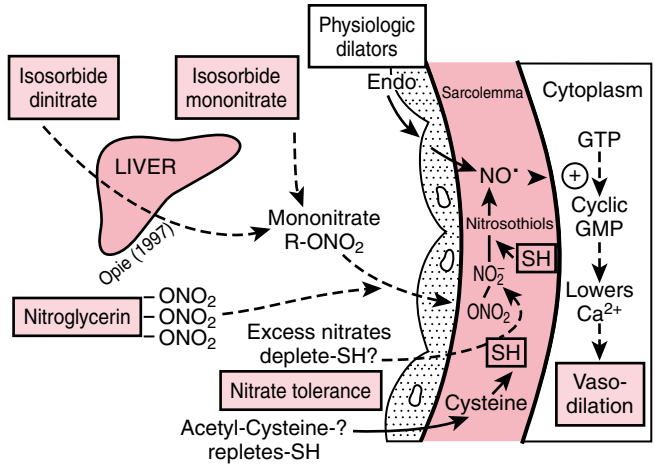

Figure 8-1 Mechanisms of the effects of nitrates in the generation of nitric oxide (NO•) and the stimulation of guanylate cyclase cyclic guanosine monophosphate (GMP), which mediates vasodilation. Sulfhydryl (SH) groups are required for the formation of NO• and the stimulation of guanylate cyclase. Isosorbide dinitrate is metabolized by the liver, whereas this route of metabolism is bypassed by the mononitrates. GTP = guanosine triphosphate. (Redrawn from Opie LH: Drugs for the Heart, 4th edition. Philadelphia, WB Saunders, 1995, p 33.)

of blood in the splanchnic capacitance system. Mesenteric blood volume increases as ventricular size, ventricular pressures, and intrapericardial pressure decrease.

NTG increases the distensibility and conductance of large arteries without changing systemic vascular resistance (SVR) at low doses. Improved compliance of the large arteries does not necessarily imply afterload reduction. At higher doses, NTG dilates smaller arterioles and resistance vessels, which reduces afterload and BP. Reductions in cardiac dimension and pressure reduce myocardial oxygen consumption ($M\dot{V}o_2$) and improve myocardial ischemia. NTG may preferentially reduce cardiac preload while maintaining systemic perfusion pressure, an important hemodynamic effect in myocardial ischemia. However, in hypovolemic states, higher doses of NTG may markedly reduce systemic BP to dangerous levels. A reflex increase in HR may occur at arterial vasodilating doses.

NTG causes vasodilation of pulmonary arteries and veins and predictably decreases right atrial (RAP), pulmonary artery (PAP), and pulmonary capillary wedge pressures (PCWP). Pulmonary artery hypertension may be reduced in various disease states and in congenital heart disease with NTG.

NTG has several important effects on the coronary circulation (Box 8-1). NTG is a potent epicardial coronary artery vasodilator in both normal and diseased vessels. Stenotic lesions dilate with NTG, reducing the resistance to coronary blood flow (CBF) and improving myocardial ischemia. Smaller coronary arteries may dilate relatively more than larger coronary vessels; however, the degree of dilation may depend on the baseline tone of the vessel. NTG effectively reverses or prevents coronary artery vasospasm.

Total CBF may initially increase but eventually decreases with NTG despite coronary vasodilation. Autoregulatory mechanisms probably result in decreases in total flow as a result of reductions in wall tension and myocardial oxygen consumption. However, regional myocardial blood flow may improve by vasodilation of intercoronary collateral vessels or reduction of subendocardial compressive forces.

BOX 8-1 ***Effects of Nitroglycerin and Organic Nitrates on the Coronary Circulation***

- Epicardial coronary artery dilation: small arteries dilate proportionately more than larger arteries
- Increased coronary collateral vessel diameter and enhanced collateral flow
- Improved subendocardial blood flow
- Dilation of coronary atherosclerotic stenoses
- Initial short-lived increase in coronary blood flow, later reduction in coronary blood flow as $M\dot{V}o_2$ decreases
- Reversal and prevention of coronary vasospasm and vasoconstriction

Modified frgom Abrams J: Hemodynamic effects of nitroglycerin and long-acting nitrates. Am Heart J 110(part 2):216, 1985.

Coronary arteriographic studies in humans demonstrate that coronary collateral vessels increase in size after NTG administration. This effect may be especially important when epicardial vessels have subtotal or total occlusive disease. Improvement in collateral flow may also be protective in situations in which coronary artery steal may occur with other potent coronary vasodilator agents. The improvement in blood flow to the subendocardium, the most vulnerable area to the development of ischemia, is secondary to both improvement in collateral flow and reductions in left ventricular end-diastolic pressure (LVEDP), which reduce subendocardial resistance to blood flow. With the maintenance of an adequate CPP (e.g., with administration of phenylephrine), NTG can maximize subendocardial blood flow. The ratio of endocardial to epicardial blood in transmural segments is enhanced with NTG. Inhibition of platelet aggregation also occurs with NTG; however, the clinical significance of this action is unknown.

Intravenous Nitroglycerin

Nitroglycerin has been available since the early 1980s as an injectable drug with a stable shelf half-life in a 400-μg/mL solution of D_5W. Blood levels are achieved instantaneously, and arterial dilating doses with resulting hypotension may quickly occur. If the volume status of the patient is unknown, initial doses of 5 to 10 μg/min are recommended. The dose necessary for relieving myocardial ischemia may vary from patient to patient, but relief is usually achieved with 75 to 150 μg/min. In a clinical study of 20 patients with rest angina, a mean dose of 72 μg/min reduced or abolished ischemic episodes in 85% of patients. However, doses as high as 500 to 600 μg/min may be necessary for ischemic relief in some patients. Arterial dilation becomes clinically apparent at doses around 150 μg/min. Drug offset after discontinuation of an infusion is rapid (2 to 5 minutes). The dosage of NTG available is less when the drug is administered in plastic bags and polyvinylchloride tubing because of NTG absorption by the bag and tubing, although this is not a significant clinical problem because the drug is titrated to effect.

Summary

Nitroglycerin remains a first-line agent for the treatment of myocardial ischemia. Special care must be taken in patients with signs of hypovolemia or hypotension, because the vasodilating effects of the drug may worsen the clinical condition. Recommendations from the ACC/AHA on intraoperative use of NTG are given in Box 8-2.

BOX 8-2 ***Recommendations for Intraoperative Nitroglycerin***

- Class I* High-risk patients previously on nitroglycerin who have active signs of myocardial ischemia without hypotension.
- Class II† As a prophylactic agent for high-risk patients to prevent myocardial ischemia and cardiac morbidity, particularly in those who have required nitrate therapy to control angina. The recommendation for prophylactic use of nitroglycerin must take into account the anesthetic plan and patient hemodynamics and must recognize that vasodilation and hypovolemia can readily occur during anesthesia and surgery.
- Class III‡ Patients with signs of hypovolemia or hypotension.

*Conditions for which there is evidence for and/or general agreement that a procedure be performed or a treatment is of benefit.

†Conditions for which there is a divergence of evidence and/or opinion about the treatment.

‡Conditions for which there is evidence and/or general agreement that the procedure is not necessary.

β-Adrenergic Blockers

β-Adrenergic blockers have multiple favorable effects in treating the ischemic heart during anesthesia (Box 8-3). They reduce oxygen consumption by decreasing HR, BP, and myocardial contractility. HR reduction increases diastolic CBF. Increased collateral blood flow and redistribution of blood to ischemic areas may occur with β-blockers. More free fatty acids may be available for substrate consumption by the myocardium. Microcirculatory oxygen delivery improves, and oxygen dissociates more easily from hemoglobin after β-adrenergic blockade. Platelet aggregation is inhibited. β-Blockers should be started early in ischemic patients in the absence of contraindications. Many patients at high risk of perioperative cardiac morbidity should be started on β-blocker therapy before surgery and continued on this therapy for up to 30 days after surgery.

Perioperative administration of β-adrenergic blockers reduces both mortality and morbidity when given to patients at high risk for coronary artery disease who must undergo noncardiac surgery.[4] These data suggest that intermediate- and high-risk patients presenting for noncardiac surgery should receive perioperative β-adrenergic blockade to reduce postoperative cardiac mortality and morbidity. Recommendations on the perioperative use of β-adrenergic blockade for noncardiac surgery are given in Box 8-4.

Physiologic Effects

ANTI-ISCHEMIC EFFECTS

β-Blockade on the ischemic heart may result in a favorable shift in the oxygen demand/supply ratio.[5] The reductions in the force of contraction and HR reduce myocardial oxygen consumption and result in autoregulatory decreases in myocardial blood flow. Several studies have shown that blood flow to ischemic regions is maintained with propranolol.

ANTIHYPERTENSIVE EFFECTS

Both β_1- and β_2-receptor blockers inhibit myocardial contractility and reduce HR; both effects should reduce BP. No acute decrease in BP occurs during acute administration of propranolol. However, chronic BP reduction has been attributed to a chronic reduction in cardiac output (CO). Reductions in high levels of plasma renin have been suggested as effective therapy in controlling essential hypertension.

ELECTROPHYSIOLOGIC EFFECTS

Generalized slowing of cardiac depolarization results from reducing the rate of diastolic depolarization (phase 4). Action potential duration and the QT interval may

BOX 8-3 ***Effects of β-Adrenergic Blockers on Myocardial Ischemia***

- Reductions in myocardial oxygen consumption
- Improvements in coronary blood flow
- Prolonged diastolic perfusion period
- Improved collateral flow
- Increased flow to ischemic areas
- Overall improvement in supply/demand ratio
- Stabilization of cellular membranes
- Improved oxygen dissociation from hemoglobin
- Inhibition of platelet aggregation
- Reduced mortality after myocardial infarction

BOX 8-4 ***Recommendations for Perioperative Medical Therapy***

- Class I β-Blockers required in the recent past to control symptoms of angina or symptomatic arrhythmias or hypertension; β-blockers: patients at high cardiac risk, owing to the finding of ischemia on preoperative testing, who are undergoing vascular surgery
- Class IIa β-Blockers: preoperative assessment identifies untreated hypertension, known coronary disease, or major risk factors for coronary disease
- Class III β-Blockers: contraindication to β-blockade

Adapted from Eagle KA, Berger PB, Calkins H, et al: ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery-executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). J Am Coll Cardiol 39:542, 2002.

shorten with β-adrenergic blockers. The ventricular fibrillation threshold is increased with β-blockers. These antiarrhythmic actions of β-blockers are enhanced in settings of catecholamine excess, such as in pheochromocytoma, acute myocardial infarction, the perioperative period, and hyperthyroidism.

Pharmacology of Intravenous β-Adrenergic Blockers

PROPRANOLOL

Propranolol has an equal affinity for β_1- and β_2-receptors, lacks intrinsic sympathomimetic activity (ISA), and has no α-adrenergic receptor activity. It is the most lipid-soluble β-blocker and generally has the most central nervous system side effects. First-pass liver metabolism (90%) is very high, requiring much higher oral doses than intravenous doses for pharmacodynamic effect.

The usual intravenous dose of propranolol initially is 0.5 to 1.0 mg titrated to effect. A titrated dose resulting in maximum pharmacologic serum levels is 0.1 mg/kg. The use of continuous infusions of propranolol has been reported after noncardiac surgery in patients with cardiac disease. A continuous infusion of 1 to 3 mg/hr can prevent tachycardia and hypertension but must be used cautiously because of the potential of cumulative effects.

METOPROLOL

Metoprolol was the first clinically used cardioselective β-blocker (Table 8-2). Its affinity for β_1-receptors is 30 times higher than its affinity for β_2-receptors, as demonstrated by radioligand binding. Metoprolol is lipid soluble, with 50% of the drug metabolized during first-pass hepatic metabolism and with only 3%

excreted renally. Protein binding is less than 10%. Metoprolol's serum half-life is 3 to 4 hours.

As with any cardioselective β-blocker, higher serum levels may result in greater incidence of β_2-blocking effects. Metoprolol is administered intravenously in 1- to 2-mg doses, titrated to effect. The potency of metoprolol is approximately one half that of propranolol. Maximum β-blocker effect is achieved with 0.2 mg/kg given intravenously.

ESMOLOL

Esmolol's chemical structure is similar to that of metoprolol and propranolol, except it has a methylester group in the para position of the phenyl ring, making it susceptible to rapid hydrolysis by red blood cell esterases (9-minute half-life). Esmolol is not metabolized by plasma cholinesterase. Hydrolysis results in an acid metabolite and methanol with clinically insignificant levels. Ninety percent of the drug is eliminated in the form of the acid metabolite, normally within 24 hours. A loading dose of 500 μg/kg given intravenously, followed by a 50- to 300- μg/kg/min infusion, will reach steady-state concentrations within 5 minutes. Without the loading dose, steady-state concentrations are reached in 30 minutes.

Esmolol is cardioselective, blocking primarily β_1-receptors. It lacks ISA and membrane-stabilizing effects and is mildly lipid soluble. Esmolol produced significant reductions in BP, HR, and cardiac index after a loading dose of 500 μg/kg and an infusion of 300 μg/kg/min in patients with coronary artery disease, and the effects were completely reversed 30 minutes after discontinuation of the infusion. Initial therapy during anesthesia may require significant reductions in both the loading and infusion doses.

Hypotension is a common side effect of intravenous esmolol. The incidence of hypotension was higher with esmolol (36%) than with propranolol (6%) at equal therapeutic endpoints. The cardioselective drugs may cause more hypotension because of β_1-induced myocardial depression and the failure to block β_2 peripheral vasodilation. Esmolol appears safe in patients with bronchospastic disease. In another comparative study with propranolol, esmolol and placebo did not change airway resistance whereas 50% of patients treated with propranolol developed clinically significant bronchospasm.

LABETALOL

Labetalol provides selective α_1-receptor blockade and nonselective β_1- and β_2-blockade. The potency of β-adrenergic blockade is 5- to 10-fold greater than α_1-adrenergic blockade. Labetalol has partial β_2-agonist effects that promote vasodilation. Labetalol is moderately lipid soluble and is completely absorbed after oral administration. First-pass hepatic metabolism is significant with production of inactive metabolites. Renal excretion of the unchanged drug is minimal. Elimination half-life is approximately 6 hours.

In contrast to other β-blockers, clinically, labetalol should be considered a peripheral vasodilator that does not cause a reflex tachycardia. BP and systolic vascular resistance decrease after an intravenous dose. Stroke volume (SV) and CO remain unchanged, with HR decreasing slightly. The reduction in BP is dose related, and acutely hypertensive patients usually respond within 3 to 5 minutes after a bolus dose of 100 to 250 μg/kg. However, the more critically ill or anesthetized patients should have their BP titrated beginning with 5- to 10-mg intravenous increments. Reduction in BP may last as long as 6 hours after intravenous dosing.

Summary

β-Adrenergic blockers are first-line agents in the treatment of myocardial ischemia. These agents effectively reduce myocardial work and oxygen demand. There is growing evidence that β-adrenergic-blocking agents may play a significant role in reducing perioperative cardiac morbidity and mortality in noncardiac surgery.[6]

Table 8-2 Properties of β-Blockers in Clinical Use

Drug	Selectivity	Partial Agonist Activity	Usual Dose for Angina
Propranolol	None	No	20 to 80 mg twice daily
Metoprolol	β_1	No	50 to 200 mg twice daily
Atenolol	β_1	No	50 to 200 mg/d
Nadolol	None	No	40 to 80 mg/d
Timolol	None	No	10 mg twice daily
Acebutolol	β_1	Yes	200 to 600 mg twice daily
Betaxolol	β_1	No	10 to 20 mg/d
Bisoprolol	β_1	No	10 mg/d
Esmolol (intravenous)	β_1	No	50 to 300 μg/kg/min
Labetalol*	None	Yes	200 to 600 mg twice daily
Pindolol	None	Yes	2.5 to 7.5 mg 3 times daily

*Labetalol is a combined α- and β-blocker.

Adapted from Gibbons RJ, Chatterjee K, Daley J, et al: ACC/AHA/ACP-ASIM Guidelines for the Management of Patients with Chronic Stable Angina: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Chronic Stable Angina). J Am Coll Cardiol 33:2092, 1999.

Calcium Channel Blockers

Calcium channel blockers reduce myocardial oxygen demands by depression of contractility, HR, and/or decreased arterial BP.[7] Myocardial oxygen supply may be improved by dilation of coronary and collateral vessels. Calcium channel blockers are used primarily for symptom control in patients with stable angina pectoris. In an acute ischemic situation, calcium channel blockers (verapamil and diltiazem) may be used for rate control in situations when β-blockers cannot be used. The most important effects of calcium channel blockers, however, may be the treatment of variant angina. These drugs can attenuate ergonovine-induced coronary vasoconstriction in patients with variant angina, suggesting protection via coronary dilation. Most episodes of silent myocardial ischemia, which may account for 70% of all transient ischemic episodes, are not related to increases in myocardial oxygen demands (HR and BP) but, rather, intermittent obstruction of coronary flow likely caused by coronary vasoconstriction or spasm. All calcium channel blockers are effective at reversing coronary spasm, reducing ischemic episodes, and reducing NTG consumption in patients with variant or Prinzmetal's angina. Combinations of NTG and calcium channel blockers, which also effectively relieve and possibly prevent coronary spasm, are at present rational therapy for variant angina. β-Blockers may aggravate anginal episodes in some patients with vasospastic angina and should be used with caution. Preservation of CBF with calcium channel blockers is a significant difference from the predominant β-blocker anti-ischemic effects of reducing myocardial oxygen consumption.

Calcium channel blockers have proven effective in controlled trials of stable angina. However, rapid-acting dihydropyridines such as nifedipine may cause a reflex tachycardia, especially during initial therapy, and exacerbate anginal symptoms. Such proischemic effects probably explain why the short-acting dihydropyridine

nifedipine in high doses produced adverse effects in patients with unstable angina. The introduction of long-acting dihydropyridines such as extended-release nifedipine, amlodipine, felodipine, isradipine, nicardipine, and nisoldipine has led to fewer adverse events. These agents should be used in combination with β-blockers. Some patients may have symptomatic relief improved more with calcium channel blockers than with β-blocker therapy.

Calcium Channels

Calcium channels are functional pores in membranes through which calcium flows down an electrochemical gradient when the channels are open. Calcium channels exist in cardiac muscle, smooth muscle, and probably many other cellular membranes. These channels are also present in cellular organelle membranes such as the sarcoplasmic reticulum and mitochondria. Calcium functions as a primary generator of the cardiac action potential and an intracellular second messenger to regulate various intracellular events.

Calcium enters cellular membranes through voltage-dependent channels or receptor-operated channels. The voltage-dependent channels depend on a transmembrane potential for activation (opening). Receptor-operated channels either are linked to a voltage-dependent channel after receptor stimulation or directly allow calcium passage through cell or organelle membranes independent of transmembrane potentials.

There are three types of voltage-dependent channels: the T (transient), L (long-lasting), and N (neuronal) channels. The T and L channels are located in cardiac and smooth muscle tissue, whereas the N channels are located only in neural tissue. The T channel is activated at low voltages (−50 mV) in cardiac tissue, plays a major role in cardiac depolarization (phase 0), and is not blocked by calcium antagonists. The L channels are the classic "slow" channels, are activated at higher voltages (−30 mV), and are responsible for phase 2 of the cardiac action potential. These channels are blocked by calcium antagonists.

Calcium channel blockers interact with the L-type calcium channel and are composed of drugs from four different classes: (1) the 1,4-dihydropyridine (DHP) derivatives (nifedipine, nimodipine, nicardipine, isradipine, amlodipine, and felodipine); (2) the phenylalkyl amines (verapamil); (3) the benzothiazepines (diltiazem); and (4) a diarylaminopropylamine ether (bepridil). The L-type calcium channel has specific receptors, which bind to each of the different chemical classes of calcium channel blockers.

Physiologic Effects

HEMODYNAMIC EFFECTS

Systemic hemodynamic effects of calcium channel blockers represent a complex interaction among myocardial depression, vasodilation, and reflex activation of the autonomic nervous system (Table 8-3).

Nifedipine, like all dihydropyridines, is a potent arterial dilator with few venodilating effects. Reflex activation of the sympathetic nervous system may increase HR. The intrinsic negative inotropic effect of nifedipine is offset by potent arterial dilation, which results in lowering of BP and increase in CO in patients. Dihydropyridines are excellent antihypertensive agents, owing to their arterial vasodilatory effects. Antianginal effects result from reduced myocardial oxygen requirements secondary to the afterload-reducing effect and to coronary vascular dilation resulting in improved myocardial oxygen delivery.

Verapamil is a less potent arterial dilator than the dihydropyridines and results in less reflex sympathetic activation. In vivo, verapamil generally results in

Table 8-3 Calcium Channel Blocker Vasodilator Potency and Inotropic, Chronotropic, and Dromotropic Effects on the Heart

	Amlodipine	Diltiazem	Nifedipine	Verapamil
Heart rate	↑/0	↓	↑/0	↓
Sinoatrial node conduction	0	↓↓	0	↓
Atrioventricular node conduction	0	↓	0	↓
Myocardial contractility	↓/0	↓	↓/0	↓↓
Neurohormonal activation	↑/0	↑	↑	↑
Vascular dilatation	↑↑	↑	↑↑	↑
Coronary flow	↑	↑	↑	↑

From Eisenberg MJ, Brox A, Bestawros AN. Calcium channel blockers: An update. Am J Med 116:35, 2004.

moderate vasodilation without significant change in HR, CO, or SV. Verapamil can significantly depress myocardial function in patients with preexisting ventricular dysfunction.

Diltiazem is a less potent vasodilator and has fewer negative inotropic effects compared with verapamil. Studies in patients reveal reductions in SVR and BP, with increases in CO, pulmonary artery wedge pressure, and ejection fraction. Diltiazem attenuates baroreflex increases in HR secondary to NTG and decreases in HR secondary to phenylephrine. Regional blood flow to the brain and kidney increases, whereas skeletal muscle flow does not change. In contrast to verapamil, diltiazem is not as likely to aggravate congestive heart failure, although it should be used carefully in these patients.

Coronary Blood Flow

Coronary artery dilation occurs with the calcium channel blockers with increases in total CBF. Nifedipine is the most potent coronary vasodilator, especially in epicardial vessels, which are prone to coronary vasospasm. Diltiazem is effective in blocking coronary artery vasoconstriction caused by a variety of agents, including α-agonists, serotonin, prostaglandin, and acetylcholine.

Electrophysiologic Effects

Calcium channel blockers exert their primary electrophysiologic effects on tissue of the conducting system that is dependent on calcium for generation of the action potential, primarily at the sinoatrial (SA) and atrioventricular (AV) nodes. They do not alter the effective refractory period of atrial, ventricular, or His-Purkinje tissue. Diltiazem and verapamil exert these electrophysiologic effects in vivo and in vitro, whereas the electrophysiologic depression of the dihydropyridines (nifedipine) is completely attenuated by reflex sympathetic activation. Nifedipine actually can enhance SA and AV node conduction, whereas verapamil and diltiazem slow conduction velocity and prolong refractoriness of nodal tissue.

Pharmacology

NIFEDIPINE

Nifedipine was the first dihydropyridine derivative to be used clinically. Other dihydropyridines available for clinical use include nicardipine, isradipine, amlodipine, felodipine, and nimodipine. In contrast to the other calcium channel blockers, nimodipine is highly lipid soluble and penetrates the blood-brain barrier. It is indicated for vascular spasm after intracerebral bleeding.

Nifedipine's oral bioavailability is approximately 70%, with peak plasma levels occurring within 30 to 45 minutes. Protein binding is 95%, and elimination half-life is approximately 5 hours. Nifedipine is available for oral administration in capsular form. The compound degenerates in the presence of light and moisture, preventing commercially available intravenous preparations. Puncture of the capsule and sublingual administration provide an onset of effects in 2 to 3 minutes.

NICARDIPINE

Nicardipine is a dihydropyridine agent with a longer half-life than nifedipine and with vascular selectivity for coronary and cerebrovascular beds. Nicardipine may be the most potent overall relaxant of vascular smooth muscle among the dihydropyridines. Peak plasma levels are reached 1 hour after oral administration, with bioavailability of 35%. Plasma half-life is 8 to 9 hours. Although the drug undergoes extensive hepatic metabolism with less than 1% of the drug excreted renally, greater renal elimination occurs in some patients. Plasma levels may increase in patients with renal failure; reduction of the dose is recommended in these patients.

Verapamil

Verapamil's structure is similar to that of papaverine. Verapamil exhibits significant first-pass hepatic metabolism, with a bioavailability of only 10% to 20%. One hepatic metabolite, norverapamil, is active and has a potency approximately 20% of that of verapamil. Peak plasma levels are reached within 30 minutes. Bioavailability markedly increases in hepatic insufficiency, mandating reduced doses. Intravenous verapamil achieves hemodynamic and dromotropic effects within minutes, peaking at 15 minutes and lasting up to 6 hours. Accumulation of the drug occurs with prolonged half-life during long-term oral administration.

Diltiazem

After oral dosing, the bioavailability of diltiazem is greater than that of verapamil, varying between 25% and 50%. Peak plasma concentration is achieved between 30 and 60 minutes, and elimination half-life is 2 to 6 hours. Protein binding is approximately 80%. As with verapamil, hepatic clearance is flow dependent and major hepatic metabolism occurs with metabolites having 40% of the clinical activity of diltiazem. Hepatic disease may require decreased dosing, whereas renal failure does not affect dosing.

Significant Adverse Effects

Most significant adverse hemodynamic effects can be predicted from the calcium channel blockers' primary effects of vasodilation and negative inotropy, chronotropy, and dromotropy. Hypotension, heart failure, bradycardia and asystole, and AV nodal block have occurred with calcium channel blockers. These side effects are more likely to occur with combination therapy with β-blockers or digoxin, in the presence of hypokalemia.

Summary

Calcium antagonists provide excellent symptom control in patients with unstable angina. In the absence of β-adrenergic blockade, the short-acting dihydropyridine nifedipine may increase the risk of myocardial infarction or recurrent angina. When β-adrenergic blockers cannot be used, and HR slowing is indicated, verapamil and diltiazem may offer an alternative.[8]

DRUG THERAPY FOR SYSTEMIC HYPERTENSION

Systemic hypertension, long recognized as a leading cause of cardiovascular morbidity and mortality, accounts for enormous health-related expenditures. Nearly a fourth of the U.S. population has hypertensive vascular disease; however, 30% of these individuals are unaware of their condition and another 30% to 50% are inadequately treated. On a worldwide basis, nearly 1 billion individuals are hypertensive. Hypertension management comprises the most common reason underlying adult visits to primary care physicians, and antihypertensive drugs are the most prescribed medication class.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7 Report) defined systolic BPs (Table 8-4) exceeding 140 mm Hg and diastolic BPs exceeding 90 mm Hg as stage 1 hypertension. BPs less than 120/80 mm Hg were defined as normal and those in between as consistent with "prehypertension."[9]

Risk for cardiovascular disease appears to increase at BPs exceeding 115/75 mm Hg, with a doubling in risk associated with each 20/10-mm Hg increment in systemic pressure. Thus, the most recent JNC-7 report recommends drug therapy for "prehypertensive" disease in patients with "compelling indications," such as chronic renal disease or diabetes. Antihypertensive therapy generally is targeted to achieve systemic BPs of less than 140/90 mm Hg; however, for high-risk patients such as those with diabetes or renal or cardiovascular disease, lower BP targets are suggested, typically less than 130/80 mm Hg.

Medical Treatment for Hypertension

More than 80 distinct medications are marketed for treatment of hypertension (Table 8-5). Often, combined therapy with two or more classes of antihypertensive medications may be needed to achieve treatment goals (Table 8-6). Although the specific drug selected for initial therapy now has been deemed less important than in the past, recognition that specific antihypertensive drug classes alleviate end-organ damage, beyond that simply associated with reductions in systemic BP, has led to targeted selection of antihypertensive drug combinations on the basis of coexisting risk factors such as recent myocardial infarction, chronic renal insufficiency, or diabetes.[10]

Management of Severe Hypertension

For purposes of characterizing treatment urgency, severe hypertension is characterized as either a hypertensive *emergency* with target organ injury (e.g., myocardial ischemia, stroke, pulmonary edema) or a hypertensive *urgency* with severe elevations in BP not yet associated with target organ damage. Chronic elevations in BP, even when of a severe nature, do not necessarily require urgent intervention and often may be managed with oral antihypertensive therapy on an outpatient basis. In contrast, a hypertensive emergency

Table 8-4 Classification and Management of Blood Pressure for Adults Aged 18 Years or Older

BP Classification	Systolic BP* (mm Hg)		Diastolic BP* (mm Hg)	Lifestyle Modification	Management* Initial Drug Therapy	
					Without Compelling Indication	*With Compelling Indication*
Normal	<120	and	<80	Encourage		
Prehypertension	120 to 139	or	80 to 89	Yes	No antihypertensive drug indicated	Drug(s) for the compelling indications†
Stage 1 hypertension	140 to 159	or	90 to 99	Yes	Thiazide-type diuretics for most; may consider ACE inhibitor, ARB, β-blocker, CCB, or combination	Drug(s) for the compelling indications Other antihypertensive drugs (diuretics, ACE inhibitor, ARB, β-blocker, CCB) as needed
Stage 2 hypertension	≥160	or	≥100	Yes	Two-drug combination for most (usually thiazide-type diuretic and ACE inhibitor or ARB or β-blocker or CCB)‡	Drug(s) for the compelling indications Other antihypertensive drugs (diuretics, ACE inhibitor, ARB, β-blocker, CCB) as needed

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BP = blood pressure; CCB = calcium channel blocker.
*Treatment determined by highest BP category.
†Treat patients with chronic kidney disease or diabetes to BP goal or < 130/80 mm Hg.
‡Initial combination therapy should be used cautiously in those at risk for orthostatic hypotension.
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Table 8-5 Oral Antihypertensive Drugs

Drug (Trade Name)	Usual Dose Range (mg/d)	Usual Daily Frequency
Thiazide Diuretics		
Chlorothiazide (Diuril)	125 to 500	1 to 2
Chlorthalidone (generic)	12.5 to 25	1
Hydrochlorothiazide (Microzide, HydroDIURIL†)	12.5 to 50	1
Polythiazide (Renese)	2 to 4	1
Indapamide (Lozol†)	1.25 to 2.5	1
Metolazone (Mykrox)	0.5 to 1.0	1
Metolazone (Zaroxolyn)	2.5 to 5	1
Loop Diuretics		
Bumetanide (Bumex†)	0.5 to 2	2
Furosemide (Lasix†)	20 to 80	2
Torsemide (Demadex†)	2.5 to 10	1
Potassium-Sparing Diuretics		
Amiloride (Midamor†)	5 to 10	1 to 2
Triamterene (Dyrenium)	50 to 100	1 to 2
Aldosterone Receptor Blockers		
Eplerenone (Inspra)	50 to 100	1
Spironolactone (Aldactone†)	25 to 50	1
β-Blockers		
Atenolol (Tenormin†)	25 to 100	1
Betaxolol (Kerlone†)	5 to 20	1
Bisoprolol (Zebeta†)	2.5 to 10	1
Metoprolol (Lopressor†)	50 to 100	1 to 2
Metoprolol extended release (Toprol XL)	50 to 100	1
Nadolol (Corgard†)	40 to 120	1
Propranolol (Inderal†)	40 to 160	2
Propranolol long-acting (Inderal LA†)	60 to 180	1
Timolol (Blocadren†)	20 to 40	2
β-Blockers with Intrinsic Sympathomimetic Activity		
Acebutolol (Sectral†)	200 to 800	2
Penbutolol (Levatol)	10 to 40	1
Pindolol (generic)	10 to 40	2
Combined α-Blockers and β-Blockers		
Carvedilol (Coreg)	12.5 to 50	2
Labetalol (Normodyne, Trandate†)	200 to 800	2
Angiotensin-Converting Enzyme Inhibitors		
Benazepril (Lotensin†)	10 to 40	1
Captopril (Capoten†)	25 to 100	2
Enalapril (Vasotec†)	5 to 40	1 to 2
Fosinopril (Monopril)	10 to 40	1
Lisinopril (Prinivil, Zestril†)	10 to 40	1
Moexipril (Univasc)	7.5 to 30	1
Perindopril (Aceon)	4 to 8	1
Quinapril (Accupril)	10 to 40	1

Table continued on following page

Table 8-5 **Oral Antihypertensive Drugs** (Continued)

Drug (Trade Name)	Usual Dose Range (mg/d)	Usual Daily Frequency
Ramipril (Altace)	2.5 to 20	1
Trandolapril (Mavik)	1 to 4	1
Angiotensin II Antagonists		
Candesartan (Atacand)	8 to 32	1
Eprosartan (Teveten)	400 to 800	1 to 2
Irbesartan (Avapro)	150 to 300	1
Losartan (Cozaar)	25 to 100	1 to 2
Olmesartan (Benicar)	20 to 40	1
Telmisartan (Micardis)	20 to 80	1
Valsartan (Diovan)	80 to 320	1 to 2
CCBs: Nondihydropyridines		
Diltiazem extended release (Cardizem CD, Dilacor XR, Tiazac†)	180 to 420	1
Diltiazem extended release (Cardizem LA)	120 to 540	1
Verapamil immediate release (Calan, Isoptin†)	80 to 320	2
Verapamil long-acting (Calan SR, Isoptin SR†)	120 to 480	1 to 2
Verapamil controlled onset, extended release (Covera HS, Verelan PM)	120 to 360	1
CCB: Dihydropyridines		
Amlodipine (Norvasc)	2.5 to 10	1
Felodipine (Plendil)	2.5 to 20	1
Isradipine (DynaCirc CR)	2.5 to 10	2
Nicardipine sustained release (Cardene SR)	60 to 120	2
Nifedipine long-acting (Adalat CC, Procardia XL)	30 to 60	1
Nisoldipine (Sular)	10 to 40	1
α_1-Blockers		
Doxazosin (Cardura)	1 to 16	1
Prazosin (Minipress†)	2 to 20	2 to 3
Terazosin (Hytrin)	1 to 20	1 to 2
Central α_2-Agonists and Other Centrally Acting Drugs		
Clonidine (Catapres†)	0.1 to 0.8	2
Clonidine patch (Catapres-TTS)	0.1 to 0.3	1 weekly
Methyldopa (Aldomet†)	250 to 1000	2
Reserpine (generic)	0.05 to 0.25	1
Guanfacine (Tenex†)	0.5 to 2	1
Direct Vasodilators		
Hydralazine (Apresoline†)	25 to 100	2
Minoxidil (Loniten†)	2.5 to 80	1 to 2

CCB = calcium channel blocker.

*In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval (trough effect). BP should be measured just before dosing to determine if satisfactory BP control is obtained. Accordingly, an increase in dosage or frequency may need to be considered. These dosages may vary from those listed in the **Physicians' Drug Reference,** 51st ed.

†Available now or soon to become available in generic preparations.

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Table 8-6 Combination Drugs for Hypertension

Combination Type	Fixed-Dose Combination (mg)*	Trade Name
ACEIs and CCB	Amlodipine-benazepril hydrochloride (2.5/10, 5/10, 5/20, 10/20)	Lotrel
	Enalapril-felodipine (5/5)	Lexxel
	Trandolapril-verapamil (2/180, 1/240, 2/240, 4/240)	Tarka
ACEIs and diuretics	Benazepril-hydrochlorothiazide (5/6.25, 10/12.5, 20/12.5, 20/25)	Lotensin HCT
	Captopril-hydrochlorothiazide (25/15, 25/25, 50/15, 50/25)	Capozide
	Enalapril-hydrochlorothiazide (5/12.5, 10/25)	Vaseretic
	Fosinopril-hydrochlorothiazide (10/12.5, 20/12.5)	Monopril/HCT
	Lisinopril-hydrochlorothiazide (10/12.5, 20/12.5, 20/25)	Prinzide, Zestoretic
	Moexipril-hydrochlorothiazide (7.5/12.5, 15/25)	Uniretic
	Quinapril-hydrochlorothiazide (10/12.5, 20/12.5, 20/25)	Accuretic
ARBs and diuretics	Candesartan-hydrochlorothiazide (16/12.5, 32/12.5)	Atacand HCT
	Eprosartan-hydrochlorothiazide (600/12.5, 600/25)	Teveten-HCT
	Irbesartan-hydrochlorothiazide (150/12.5, 300/12.5)	Avalide
	Losartan-hydrochlorothiazide (50/12.5, 100/25)	Hyzaar
	Olmesartan medoxomil-hydrochlorothiazide (20/12.5, 40/12.5, 40/25)	Benicar HCT
	Telmisartan-hydrochlorothiazide (40/12.5, 80/12.5)	Micardis-HCT
	Valsartan-hydrochlorothiazide (80/12.5, 160/12.5, 160/25)	Diovan-HCT
BBs and diuretics	Atenolol-chlorthalidone (50/25, 100/25)	Tenoretic
	Bisoprolol-hydrochlorothiazide (2.5/6.25, 5/6.25, 10/6.25)	Ziac
	Metoprolol-hydrochlorothiazide (50/25, 100/25)	Lopressor HCT
	Nadolol-bendroflumethiazide (40/5, 80/5)	Corzide
	Propranolol LA-hydrochlorothiazide (40/25, 80/25)	Inderide LA
	Timolol-hydrochlorothiazide (10/25)	Timolide
Centrally acting drug and diuretic	Methyldopa-hydrochlorothiazide (250/15, 250/25, 500/30, 500/50)	Aldoril
	Reserpine-chlorthalidone (0.125/25, 0.25/50)	Demi-Regroton, Regroton

Table continued on following page

Table 8-6 **Combination Drugs for Hypertension** (Continued)

Combination Type	Fixed-Dose Combination (mg)*	Trade Name
	Reserpine-chlorothiazide (0.125/250, 0.25/500)	Diupres
	Reserpine-hydrochlorothiazide (0.125/25, 0.125/50)	Hydropres
Diuretic and diuretic	Amiloride-hydrochlorothiazide (5/50)	Moduretic
	Spironolactone-hydrochlorothiazide (25/25, 50/50)	Aldactazide
	Triamterene-hydrochlorothiazide (37.5/25, 75/50)	Dyazide, Maxzide

BB = β-blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; CCB = calcium channel blocker.

*Some drug combinations are available in multiple fixed doses. Each drug dose is reported in milligrams.

Adapted with permission from Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC-7 Report. JAMA 289:2560, 2003.

necessitates immediate therapeutic intervention, most often in an intensive care setting, with intravenous antihypertensive therapy and invasive arterial BP monitoring. In the most extreme cases of *malignant hypertension,* severe elevations in BP may be associated with retinal hemorrhages, papilledema, and evidence of encephalopathy, which may include headache, vomiting, seizure, and/or coma. Progressive renal failure and cardiac decompensation are additional clinical features characteristic of the most severe hypertensive emergencies.

The favored parenteral drug for rapid treatment of hypertensive emergencies remains sodium nitroprusside (Table 8-7). An NO donor, sodium nitroprusside induces arterial and venous dilation, providing rapid and predictable reductions in systemic BP. Prolonged administration of large doses may be associated with cyanide or thiocyanate toxicity; however, this is rarely a concern in the setting of acute hypertensive emergencies. Although less potent and predictable than sodium nitroprusside, NTG, another NO donor, may be preferable in the setting of myocardial ischemia or after coronary artery bypass grafting (CABG). NTG preferentially dilates venous capacitance beds as opposed to arterioles; however, rapid onset of tolerance limits the efficacy of sustained infusions to maintain BP control. Nicardipine, a parenteral dihydropyridine calcium channel blocker, and fenoldopam, a selective dopamine-1 (D_1)-receptor antagonist, have been utilized increasingly in select patient populations after CABG and in the setting of renal insufficiency, respectively.[11]

Several drugs remain available for intermittent parenteral administration in the setting of hypertensive emergencies or urgencies. Hydralazine, labetalol, and esmolol provide additional therapeutic options for intermittent parenteral injection for hypertensive control.

PHARMACOTHERAPY FOR ACUTE AND CHRONIC HEART FAILURE

Chronic heart failure is one major cardiovascular disorder that continues to increase in incidence and prevalence, both in the United States and worldwide. It affects nearly 5 million persons in the United States, and roughly 550,000 new cases are diagnosed each year.[12] Currently, 1% of those 50 to 59 years of age and 10% of individuals older than

80 have heart failure. Because heart failure is primarily a disease of the elderly, its prevalence is projected to increase twofold to threefold over the next decade, as the median age of the U.S. population continues to increase. The increasingly prolonged survival of patients with various cardiovascular disorders that culminate in ventricular dysfunction (e.g., patients with coronary artery disease are living longer rather than dying acutely with myocardial infarction) further compounds the heart failure epidemic. Despite improvements in the understanding of the neurohormonal mechanisms underlying its pathophysiology and remarkable advances made in pharmacologic therapy, heart failure continues to cost the United States an estimated $38 billion annually in medical expenditures, and it contributes to approximately 250,000 deaths per year. Given the public health impact of the disease and the rapid pace of therapeutic advances, it is essential that the perioperative physician remain aware of contemporary clinical practice for the benefit of those patients with chronic heart failure presenting to the operating room or intensive care unit.

Heart Failure Classification

The ACC/AHA updated guidelines for evaluating and managing heart failure include a new, four-stage classification system emphasizing both the evolution and progression of the disease (Box 8-5). It calls attention to patients with preclinical stages of heart failure to focus on halting disease progression. The staging system is meant to complement, not replace, the widely used New York Heart Association (NYHA) classification, a semiquantitative index of functional classification that categorizes patients with heart failure by the severity of their symptoms. The NYHA classification remains useful clinically because it reflects symptoms, which in turn correlate with quality of life and survival. The new classification system for heart failure, recognizing its progressive course and identifying those who are at risk, reinforces the importance of determining the optimal strategy for neurohormonal antagonism in an attempt to improve the natural history of the syndrome.

Heart failure remains the final common pathway for coronary artery disease, hypertension, valvular heart disease, and cardiomyopathy, in which the natural history results in symptomatic or asymptomatic left ventricular dysfunction. The neurohormonal responses to impaired cardiac performance (salt and water retention, vasoconstriction, sympathetic stimulation) are initially adaptive but, if sustained, become maladaptive, resulting in pulmonary congestion and excessive afterload. This, in turn, leads to a vicious cycle of increases in cardiac energy expenditure and worsening of pump function and tissue perfusion (Table 8-8). Although the cardiorenal and cardiocirculatory branches of this neurohormonal hypothesis of heart failure were the original foundation for the use of diuretics, vasodilators, and inotropes, respectively, seminal information in the early 1990s emerged from large, randomized clinical trials that showed angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers, but not most other vasodilators, prolonged survival in patients with heart failure. In a similar fashion, the use of β-blockers, despite their negative inotropic effects, improved morbidity and mortality in randomized controlled trials.

The finding that low-dose aldosterone antagonists added to conventional therapy for heart failure reduced mortality in patients with severe heart failure suggests that there is more to the neurohormonal hypothesis of drug efficacy than cardiorenal and hemodynamic effects alone. Taken together with evidence from basic investigations showing that Ang II is a growth factor and a vasoconstrictor, the clinical data promoted a shift in focus from cardiorenal and cardiocirculatory processes toward cardiac remodeling as the central component in the progression of this neurohormone-mediated cardiac syndrome.[13] The renin-angiotensin-aldosterone system (RAAS), excess sympathetic activity, endothelin, and various cytokines all have been implicated as stimuli of proliferative signaling that contribute to maladaptive cardiac growth.

Table 8-7 **Parenteral Drugs for Treatment of Hypertensive Emergencies***

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BOX 8-5 *ACC/AHA Four-Stage Classification and Management Recommendations*

Stage A High risk for developing heart failure. No structural or functional disorders of the heart. No symptoms of heart failure.

Examples Hypertension; coronary artery disease; diabetes mellitus; history of cardiotoxic therapy or alcohol abuse; history of rheumatic heart disease; family history of cardiomyopathy

Treatment Emphasize prevention: treat hypertension, encourage smoking cessation, treat dyslipidemia, encourage regular exercise; discourage excessive alcohol use or illicit drug use. Consider ACE inhibitor for patients with history of peripheral vascular disease, diabetes mellitus, or hypertension with associated risk factors.

Stage B Structural heart disease strongly associated with heart failure. No symptoms of heart failure.

Examples Patients with left ventricular hypertrophy or fibrosis, left ventricular dilatation or hypocontractility, asymptomatic valvular heart disease, or previous myocardial infarction.

Treatment Use all preventive measures listed under stage A. ACE inhibitors and/or β-blockers are recommended for patients with recent or remote history of myocardial infarction. Consider the same for patients with reduced ejection fraction, regardless of previous myocardial infarction history.

Stage C Structural heart disease with prior or current symptoms of heart failure.

Examples Patients with dyspnea or fatigue due to left ventricular systolic dysfunction; asymptomatic patients who are undergoing treatment for prior symptoms of heart failure.

Treatment Use all measures listed in stage A. Drugs recommended for routine use include loop diuretics, ACE inhibitors, β-blockers, and digitalis. Advise dietary salt restriction.

Stage D Advanced structural heart disease. Marked symptoms of heart failure at rest despite maximal medical therapy.

Examples Patients who are often hospitalized for heart failure and who cannot be safely discharged from the hospital; patients in the hospital awaiting heart transplantation; patients at home receiving continuous intravenous support for symptom relief or being supported with a mechanical circulatory assist device; patients in a hospice setting for the management of heart failure. Specialized interventions are required.

Treatment Use all measures listed under Stages A, B, and C. Specialized interventions include mechanical assist devices, heart transplantation, continuous intravenous inotropic infusions for palliation, hospice care.

ACE = angiotensin-converting enzyme; LV = left ventricular.

β-Blockers are relatively contraindicated in patients with bronchospastic pulmonary disease.

Adapted from permission from Clinical update: New guidelines for evaluating and managing heart failure. Women's Health in Primary Care 5(2):105, 2002.

Table 8-8 Neurohormonal Effects of Impaired Cardiac Performance on the Circulation

Response	Short-Term Effects	Long-Term Effects
Salt and water retention	Augments preload	Pulmonary congestion, edema
Vasoconstriction	Maintains blood pressure for perfusion of vital organs	Exacerbates pump dysfunction (excessive afterload), increases cardiac energy expenditure
Sympathetic stimulation	Increases heart rate and ejection	Increases energy expenditure

Modified from Katz AM: Heart failure. In Fozzard HA, Haber E, Jennings RB: The Heart and Cardiovascular System: Scientific Foundations, 2nd ed. New York, Raven, 1992, pp 333-353.

BOX 8-6 ***Mechanical Disadvantage Created by Left Ventricular Remodeling***

- Increased wall stress (afterload)
- Afterload mismatch
- Episodic subendocardial hypoperfusion
- Increased oxygen utilization
- Sustained hemodynamic overloading
- Worsening activation of compensatory mechanisms

Adapted from Mann DL: Mechanisms and models in heart failure: an combinatorial approach. Circulation 100:999–1008, 1999.

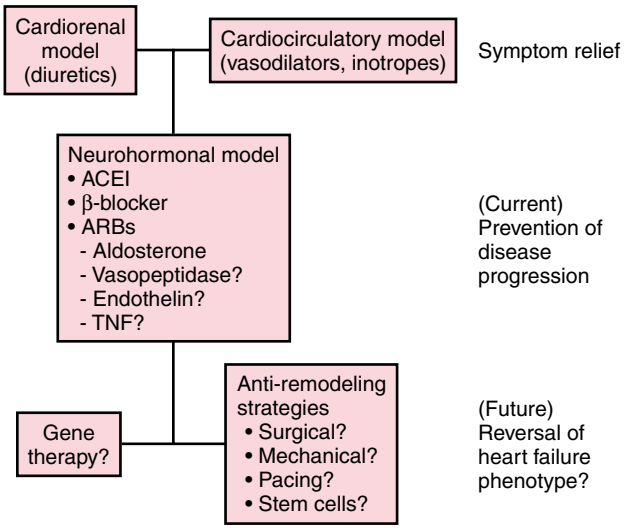

Figure 8-2 Current and future treatments of heart failure. Currently, heart failure therapies are focused on prevention of disease progression with drugs that antagonize neurohormonal systems. Future therapies may involve antagonists of other biologically active systems (e.g., endothelins, TNFα) and anti-remodeling strategies that may reverse the heart failure phenotype. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; NEP = neutral endopeptidase blocker. (Adapted from Mann DL. Mechanisms and model in heart failure: A combinatorial approach. Circulation 100:999, 1999.)

Accordingly, ventricular remodeling, or the structural alterations of the heart in the form of dilatation and hypertrophy (Box 8-6), in addition to the counterregulatory hemodynamic responses, lead to progressive ventricular dysfunction and represent the target of current therapeutic interventions (Fig. 8-2).

Pathophysiologic Role of the Renin-Angiotensin System in Heart Failure

The renin-angiotensin system (RAS) is one of several neuroendocrine systems that are activated in patients with heart failure. The RAS is also an important mediator in the progression of heart failure. In the short term, the juxtaglomerular cells of the kidney release the proteolytic enzyme renin in response to a decrease in BP or renal perfusion (e.g., hemorrhage) generating Ang I from circulating angiotensinogen. ACE cleavage of Ang II from Ang I in the lung produces circulating Ang II. Acutely, Ang II acts as a

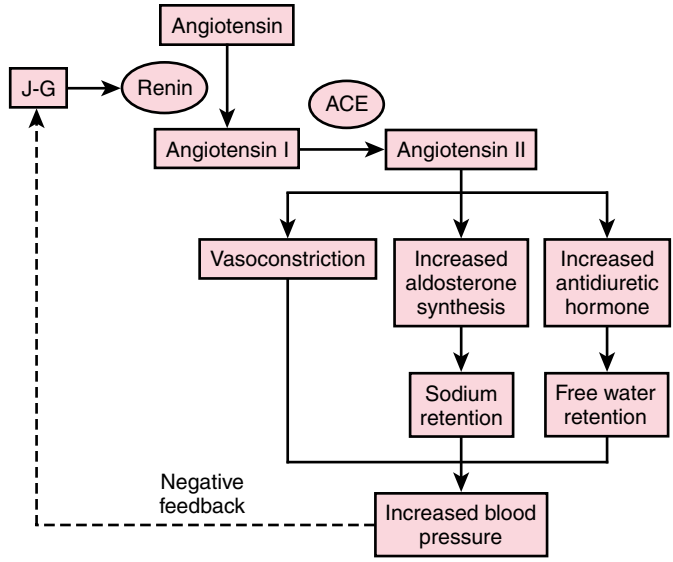

Figure 8-3 Basic pathway of the renin-angiotensin-aldosterone system (RAAS). (From Jaski BE: Basis of Heart Failure: A Problem Solving Approach. Boston, Kluwer Academic Publishers, 2000, with kind permission of Springer Science and Business Media.)

potent arteriolar and venous vasoconstrictor to return BP and filling pressure to baseline, respectively. Ang II also stimulates the release of aldosterone from the adrenal cortex and antidiuretic hormone from the posterior pituitary. Both contribute to increases in blood volume through their effects on the kidney to promote salt and water reabsorption, respectively. In the long term, elevations in Ang II lead to sodium and fluid retention and increases in systemic vascular resistance, which contribute to symptoms of heart failure, pulmonary congestion, and hemodynamic decompensation (Fig. 8-3).

In addition to these cardiorenal and cardiocirculatory effects, most of the hormones and receptors of the RAS are expressed in the myocardium, where they contribute to maladaptive growth or remodeling, a key factor in the progression of heart failure. Increased expression of mRNA for angiotensinogen, ACE, and Ang II has been identified in the failing human heart. Correspondingly, increased coronary sinus Ang II concentrations were measured in patients with dilated and ischemic cardiomyopathy, signifying a paracrine or autocrine action of the RAS. Moreover, progressive increases in coronary sinus Ang II production correlated with increases in NYHA functional classification of heart failure. Taken together, these data provide evidence that intracardiac RAS is involved in the evolution of the disease process.

The effects of Ang II on its receptors AT_1 and AT_2 are well appreciated. The AT_1 receptor is involved in several effects that lead to adverse cardiovascular outcomes. Activation of AT_1 receptors promotes aldosterone and vasopressin secretion with concomitant increases in salt and water reabsorption through the kidneys, vasoconstriction, catecholamine release, and cell growth and proliferation of cardiovascular tissue. Stimulation of AT_2 receptors, on the other hand, results in natriuresis, vasodilation, release of bradykinin and NO, and cell growth inhibition or apoptosis. The Ang II that is formed locally in the heart acts primarily through AT_1 receptors located on myocytes and fibroblasts where it participates in the regulation of cardiac remodeling. Through complex cascades of intracellular signal transduction that activate protein transcription factors within the nucleus initiating the creation of RNA transcripts, the long-term effects of intracardiac Ang II on the AT_1 receptor

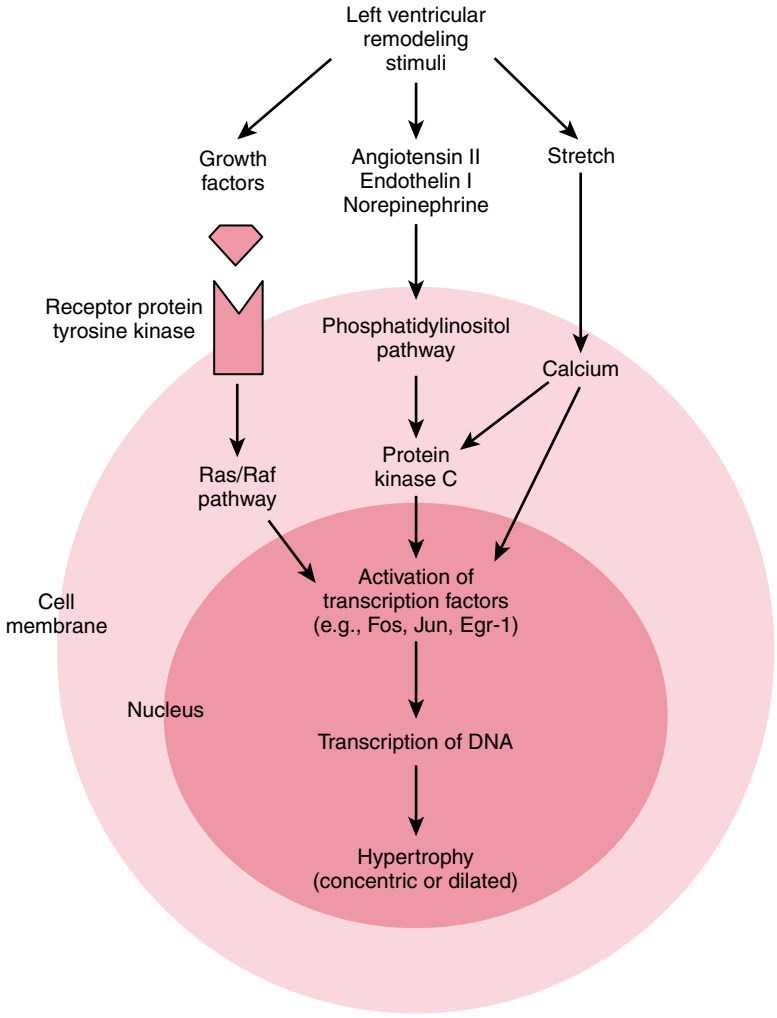

Figure 8-4 Left ventricular remodeling stimuli.

result in cardiomyocyte hypertrophy, fibroblast proliferation, and extracellular matrix deposition (Fig. 8-4). These processes contribute to progressive left ventricular remodeling and left ventricular dysfunction characteristic of heart failure.

Angiotensin-Converting Enzyme Inhibitors

CLINICAL EVIDENCE

Evidence supporting the beneficial use of ACE inhibitors in patients with heart failure comes from various randomized, placebo-controlled clinical trials (Table 8-9). Initially this class of drugs was evaluated for treatment of symptomatic heart failure (SOLVD, V-HeFT, CONSENSUS). Patients with NYHA class II to IV heart failure treated with ACE inhibitors had reductions in mortality ranging from 16% to 31%. Subsequently, ACE inhibitors were also found to improve outcome for asymptomatic patients with left ventricular systolic dysfunction in

Table 8-9 Selected Clinical Trials of Angiotensin-Converting Enzyme Inhibitors in Heart Failure

Patient Subset	Heart Failure Stage	Drug	Trial
Heart Failure			
NYHA Class II-III	C	Enalapril	SOLVD (treat); V-HeFT II
NYHA Class IV	D	Enalapril	CONSENSUS I
Asymptomatic Left Ventricular Dysfunction			
Ejection fraction < 35%	B	Enalapril	SOLVD (prevent)
Post–myocardial infarction (ejection fraction < 40%)	B	Captopril	SAVE
Acute myocardial infarction	B	Captopril	GISSI
		Lisinopril	ISIS-4
Asymptomatic High Risk (history of diabetes mellitus, pulmonary vascular disease, and coronary risk factors)	A	Ramipril	HOPE

the following categories: patients with ejection fractions less than 35% due to cardiomyopathy, patients within 2 weeks after myocardial infarction with ejection fractions less than 40%, and patients presenting within the first 24 hours of myocardial infarction regardless of ejection fraction. Results from the Heart Outcomes Prevention Evaluation (HOPE) study have further expanded the indications for this class of agents to include asymptomatic, high-risk patients to prevent new-onset heart failure.[14] In patients with diabetes or peripheral vascular disease and an additional atherosclerotic risk factor, but without clinical heart failure or systolic dysfunction, ramipril (10 mg/day) reduced the heart failure risk by 23%. Together, these data endorse the use of ACE inhibitors as first-line therapy for a broad spectrum of patients, including those with left ventricular systolic dysfunction, with or without symptoms, and in high-risk patients with vascular disease and/or diabetes, in addition to those with the traditional coronary risk factors. Since the beginning of these trials, the rationale for the use of ACE inhibitors has expanded from a reduction in the progression of clinical heart failure through ACE inhibitor–mediated vasodilatory action to acknowledgment that ACE inhibitors also directly affect the cellular mechanisms responsible for progressive myocardial pathology.

MECHANISMS OF ACTION

ACE inhibitors act by inhibiting one of several proteases responsible for cleaving the decapeptide, Ang I, to form the octapeptide Ang II. Because ACE is also the enzyme that degrades bradykinin, ACE inhibitors lead to increased circulating and tissue levels of bradykinin (Fig. 8-5). ACE inhibitors have several useful effects in chronic heart failure. They are potent vasodilators through decreasing Ang II and norepinephrine and increasing bradykinin, NO, and prostacyclin. By reducing the secretion of aldosterone and antidiuretic hormone (ADH), ACE inhibitors also reduce salt and water reabsorption

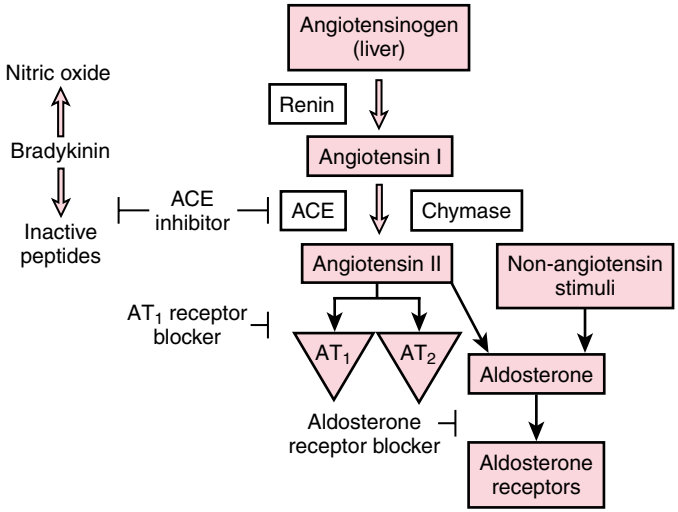

Figure 8-5 Activation of the renin-angiotensin-aldosterone system (RAAS). (Redrawn from Mann DL. Heart Therapy: A Companion to Braunwald's Heart Disease. Philadelphia: Saunders, 2004.)

from the kidney. ACE inhibitors reduce release of norepinephrine from sympathetic nerves by acting on AT_1 receptors at the nerve terminal. Within tissue, ACE inhibitors inhibit Ang II production and thus attenuate Ang II-mediated cardiomyocyte hypertrophy and fibroblast hyperplasia. Clinical evidence supporting an ACE inhibitor-mediated role in cardiac remodeling comes from comparative studies of enalapril versus placebo (SOLVD trial) and enalapril versus hydralazine isosorbide dinitrate (VHeft II trial).

ACE inhibitors attenuate insulin resistance, a common metabolic abnormality in heart failure patients, independent of Ang II activity. Ang II receptor antagonists do not attenuate insulin resistance. Both ACE inhibitors and angiotensin-receptor blockers have been shown to reduce proteinuria, and slow the progression to renal failure in hypertensives (and a common comorbidity in heart failure patients).

Angiotensin II Receptor Blockers for Heart Failure

PATHOPHYSIOLOGY/MECHANISM OF ACTION

Although ACE inhibitors reduce mortality, many patients will not tolerate their side effects. ACE inhibitors incompletely antagonize Ang II. These factors have prompted the development of specific Ang II receptor blockers in the pharmacologic treatment of heart failure. Non–ACE-generated Ang II within the myocardium contributes to left ventricular remodeling and progression of heart failure through AT_1 receptor effects. Selective AT_1 blockers prevent Ang II from acting on the cell, preventing vasoconstriction, sodium retention, and release of norepinephrine and delaying or preventing left ventricular hypertrophy and fibrosis. AT_2 receptors remain unaffected, and their actions, including NO release, remain intact.[15]

CLINICAL PRACTICE

Angiotensin-receptor blockers may be used as alternatives to ACE inhibitors for the treatment of patients with symptomatic heart failure if there are side effects to ACE inhibitors (e.g., persistent cough, angioedema, hyperkalemia, or worsening renal dysfunction) or persistent hypertension despite ACE inhibitors and β-blockers. Because ARBs do not affect bradykinin levels, cough and angioedema are rare side effects.

Aldosterone Receptor Antagonists

Aldosterone, a mineralocorticoid, is another important component of the neurohormonal hypothesis of heart failure. Although it was previously assumed that treatment with an ACE inhibitor (or ARB) would block the production of aldosterone in patients with heart failure, elevated levels of aldosterone have been measured despite inhibition of Ang II. Adverse effects of elevated aldosterone levels on the cardiovascular system include sodium retention, potassium and magnesium loss, ventricular remodeling (e.g., collagen production, myocyte growth, and hypertrophy), myocardial norepinephrine release, and endothelial dysfunction.

CLINICAL EVIDENCE

Two large-scale trials have demonstrated improved outcomes with aldosterone-receptor antagonism in chronic heart failure. The Randomized Aldactone Evaluation Study (RALES), conducted in more than 1600 symptomatic heart failure (e.g., stage C, NYHA III-IV) patients, showed the efficacy of spironolactone (26 mg/day) (in combination with standard therapy: ACE inhibitor, loop diuretic with or without digoxin and a β-blocker). Eplerenone is a new aldosterone antagonist that lacks some of spironolactone's common side effects. The Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHSUS), conducted in more than 6600 patients with symptomatic heart failure within 3 to 14 days after myocardial infarction, showed that eplerenone (25 to 50 mg/day) in combination with ACE inhibitor, loop diuretic, and β-blocker reduced all-cause mortality ($P = .008$), death from cardiovascular causes ($P = .0002$), and hospitalization for cardiovascular events.[16,17]

β-Adrenergic Receptor Antagonists

Sympathetic Nervous System Activation and Its Role in the Pathogenesis of Heart Failure

Activation of the sympathetic nervous system (SNS) (e.g., after myocardial infarction or with long-standing hypertension), much like increases in RAS activity, contributes to the pathophysiology of heart failure. In brief, SNS activation leads to pathologic left ventricular growth and remodeling. Myocytes thicken and elongate, with eccentric hypertrophy and increases in sphericity. Wall stress is increased by this architecture, promoting subendocardial ischemia, cell death, and contractile dysfunction. There is downregulation of calcium regulatory proteins, including sarcoplasmic reticulum calcium ATPase, and impairment of contractility and relaxation. The activated SNS can also be harmful to myocytes directly through programmed cell death. As myocytes are replaced by fibroblasts, the heart function deteriorates from this "remodeling." The threshold for arrhythmias may also be lowered, contributing in a vicious, deteriorating cycle.

How β-Adrenergic Receptor Blockers Influence the Pathophysiology of Heart Failure

In chronic heart failure, the beneficial effects of long-term β-blockade include improved systolic function and myocardial energetics and reversal of pathologic remodeling. A shift in substrate utilization from free fatty acids to glucose, a more efficient fuel in the face of myocardial ischemia, may partly explain the improved energetics and mechanics in the failing heart treated with β-blockade. Heart rate, a major determinant of myocardial oxygen consumption, is reduced by β_1-receptor blockade.

CLINICAL EVIDENCE

The use of β-blockers in patients with heart failure was initially accepted with skepticism related to the perceived risk of decompensation from transient negative inotropic effects. However, data from both human and animal studies have shown that β-blockers improve energetics and ventricular function and reverse pathologic chamber remodeling. Although this beneficial biologic process takes 3 months or more to manifest, it translates into improved outcomes (reduced deaths and hospitalizations) in patients with heart failure. The available randomized trials show that metoprolol CR/XL, bisoprolol, and carvedilol (in conjunction with ACE inhibitors) reduce morbidity (hospitalizations) in symptomatic, stage C and D (not in cardiogenic shock) heart failure patients (NYHA II-IV class).

β-Blockers are classified as being first-, second-, or third-generation drugs based on specific pharmacologic properties. First-generation agents, such as propranolol and timolol, block both β_1- and β_2-adrenoreceptors, are considered nonselective, and have no ancillary properties. Second-generation agents, such as metoprolol, bisoprolol, and atenolol, are specific for the β_1-adrenoreceptor subtype but lack additional mechanisms of cardiovascular activity. Third-generation agents, such as bucindolol, carvedilol, and labetalol, block both β_1- and β_2-adrenoreceptors as well as possessing vasodilatory and other ancillary properties. Specifically, labetalol and carvedilol produce vasodilation by α_1-adrenoreceptor antagonism.

CLINICAL PRACTICE

Current evidence suggests that β-blockers should be given to all heart failure patients with reduced ejection fraction (<0.40) who are stabilized on oral medications including ACE inhibitors and diuretics, unless there is a contraindication. This recommendation is endorsed by the ACC/AHA and the European Society of Cardiology. Specifically, long-term β-blockade is advocated in stage B-D heart failure patients in addition to ACE inhibition to limit disease progression and reduce mortality. Patients with ongoing decompensation (e.g., requiring intravenous inotropic or vasodilator therapy), overt fluid retention, or symptomatic hypotension should not receive β-blockers. There is no apparent decline in safety or efficacy when β-blockers are given to diabetics with heart failure. The long-term benefit of β-blocker therapy in patients with coexisting chronic obstructive pulmonary disease is uncertain, because these patients have been excluded from the major clinical trials.

The three agents with clinical trial evidence for improved morbidity and mortality in patients with heart failure are carvedilol, metoprolol CR/XL, and bisoprolol.[18] Starting doses of β-blockers should be small to minimize worsening of heart failure symptoms, hypotension, and bradycardia. The dose should be doubled every 1 to 2 weeks, as tolerated, until target doses shown to be effective in large trials are achieved. Although it is recommended that β-blocker therapy be continued indefinitely in patients with heart failure, if it is to be electively stopped, a slow downtitration is preferred. Acute withdrawal of β-blocker therapy in the face of high adrenergic tone may result in sudden cardiac death. The adverse effects of β-blocker therapy include fatigue, dizziness, hypotension, and bradycardia. Because the absolute risk of adverse events is small compared with the overall risk reduction of cardiovascular death, few patients have been withdrawn from β-blocker therapy.

Adjunctive Drugs

In addition to ACE inhibitors and β-blockers, diuretics and digoxin are often prescribed for patients with left ventricular systolic dysfunction and symptomatic heart failure.

Diuretics

For most patients, volume status should be optimized before introduction of β-blockers and ACE inhibitors. Patients with pulmonary congestion often will require a loop diuretic in addition to standard therapy. Diuretics relieve dyspnea, decrease heart size and wall stress, and correct hyponatremia of volume overload. However, overly aggressive and especially unmonitored diuretic therapy can lead to metabolic abnormalities, intravascular depletion, hypotension, and neurohormonal activation.

Digoxin

Digoxin continues to be useful for patients with symptomatic heart failure and left ventricular systolic dysfunction despite receiving ACE inhibitor, β-blocker, and diuretic therapy. Digoxin is the only positive inotropic drug approved for the management of chronic heart failure. Its indirect mechanism of positive inotropy begins with inhibition of the myocardial sarcolemmal Na^+-K^+ ATPase, resulting in increased intracellular Na^+. This, in turn, prompts the Na^+/Ca^{2+} exchanger to extrude Na^+ from the cell, increasing intracellular Ca^{2+}. The increased Ca^{2+} now available to the contractile proteins increases contractile function. Besides its inotropic effects, digoxin has important vagotonic and sympatholytic effects. In atrial fibrillation, digoxin slows the rate of conduction at the AV node. In heart failure patients it reduces sympathetic efferent nerve activity to the heart and peripheral circulation through direct effects on the carotid sinus baroreceptors. Digoxin increases HR variability, an additional beneficial action on autonomic function in the patient with heart failure. Although these properties are beneficial in controlling the ventricular rate in atrial fibrillation, digoxin has only a narrow therapeutic/toxicity ratio. Digoxin toxicity is dose dependent and modified by concurrent medications (non–potassium-sparing diuretics) or conditions (renal insufficiency, myocardial ischemia). Ventricular arrhythmias consequent to digoxin toxicity may be caused by calcium-dependent afterpotentials. In patients with intoxication and life-threatening arrhythmias, purified anti-digoxin FAB fragments from digoxin-specific antisera provide a specific antidote.

The efficacy of digoxin for symptomatic heart failure was shown in randomized, controlled trials. The Digitalis Investigators Group (DIG) trial, enrolling more than 6500 patients with an average follow-up of 37 months, showed that digoxin reduced the incidence of heart failure exacerbations. Although the study showed no difference in survival in patients with an ejection fraction less than 45% receiving either digoxin or placebo, the combined endpoint of death or hospitalization for heart failure was significantly reduced in patients who received digoxin (27% vs. 35%; relative risk, 0.72; 95% confidence interval, 0.66 to 0.79). Efficacy of digoxin in patients with mildly symptomatic heart failure was shown in pooled results from the Prospective Randomized Study of Ventricular Function (PROVED) and the Randomized Assessment of Digoxin and Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) trials. Patients randomized to digoxin withdrawal had an increased likelihood of treatment failure compared with those who continued to receive digoxin, suggesting that patients with left ventricular systolic dysfunction benefit from digoxin (or, at least, do *not* benefit from digoxin withdrawal), even when they have only mild symptoms. Accordingly, digoxin is recommended for symptomatic heart failure unless contraindicated. Together with ACE inhibitors, β-blockers, and diuretics, digoxin should be added to the therapeutic armamentarium. Ideally, serum digoxin concentration should remain between 0.7 and 1.1 ng/mL. In the elderly patient with renal insufficiency, severe conduction abnormalities, or acute coronary syndromes, even a low dose of 0.125 mg/day should be used with extra caution.[19]

Future Therapy

Among the promising nonpharmacologic therapies for the management of heart failure are the implantable defibrillators and biventricular pacemakers. In the COMPANION trial (The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure), cardiac resynchronization therapy with a pacemaker combined with an implantable defibrillator significantly decreased the likelihood of death from or hospitalization for heart failure when compared with conventional pharmacologic therapy.[20]

Stem cell therapy is another potential treatment of heart failure. Stem cell therapy has shown promise in the treatment of ischemic heart disease both in the laboratory and in small clinical studies. Autologous bone marrow and peripheral blood stem cells transplanted in patients with acute myocardial infarction improved cardiac function. However, until double-blind, randomized controlled trials are performed, the true benefit of this innovative treatment remains unknown.

Management of Acute Exacerbations of Chronic Heart Failure

Patients with chronic heart failure, despite good medical management, may experience episodes of pulmonary edema or other signs of acute volume overload. These patients may require hospitalization for intensive management if diuretics fail to relieve their symptoms. Other patients may experience exacerbations of heart failure associated with acute myocardial ischemia or infarction, worsening valvular dysfunction, infections (including myocarditis), or failure to maintain an established drug regimen. Fonarow and associates described a risk stratification system for in-hospital mortality in acutely decompensated heart failure using data from a national registry. Low-, intermediate-, and high-risk patients with mortality ranging from 2.1% to 21.9% were identified using blood urea nitrogen, creatinine, and systolic BP on admission. These patients will require all the standard medications, as outlined in previous sections, and may also require infusions of vasodilators or positive inotropic drugs.[21]

Vasodilators

Intravenous vasodilators have long been used to treat the symptoms of low CO in patients with decompensated chronic heart failure. In general, vasodilators reduce ventricular filling pressures and SVR while increasing SV and CO. NTG is commonly used for this purpose and has been studied in numerous clinical trials. It is often initially effective at relatively small doses (20 to 40 μg/min) but frequently requires progressively increasing doses to counteract tachyphylaxis. NTG is associated with dose-dependent arterial hypotension.

Nesiritide

Brain natriuretic peptide (BNP) is a 32-amino acid peptide that is mainly secreted from the cardiac ventricles. Physiologically, BNP functions as a natriuretic and diuretic. It also serves as a counterregulatory hormone to Ang II, norepinephrine, and endothelin by decreasing the synthesis of these agents and by direct vasodilation.

As the clinical severity of heart failure increases, the concentrations of BNP in blood also increase. As a result, measurements of BNP in blood have been used to evaluate new onset of dyspnea (to distinguish between lung disease and heart failure). BNP concentrations in blood increase with decreasing left ventricular ejection fraction; therefore, measurements of this mediator have been used to estimate prognosis.

BNP concentrations decline in response to therapy with ACE inhibitors, Ang II antagonists, and aldosterone antagonists.

In addition, recombinant BNP has been released as a drug (nesiritide) indicated for patients with acute heart failure and dyspnea with minimal activity. Nesiritide produces arterial and venous dilatation through increasing cGMP. Nesiritide does not increase HR and has no effect on cardiac inotropy. It has a rapid onset of action and a short elimination half-life (15 minutes). In clinical studies, loading doses have ranged from 0.25 to 2 μg/kg and maintenance doses have ranged from 0.005 to 0.03 μg/kg/min. Studies have shown that nesiritide reduces symptoms of acute decompensated heart failure similarly to NTG, without development of acute tolerance. Patients receiving nesiritide experienced fewer adverse events than those receiving NTG. However, the mortality rate at 6 months was higher in the patients receiving nesiritide than in the NTG group.[22] Compared with dobutamine, nesiritide was associated with fewer instances of ventricular tachycardia or cardiac arrest.

Inotropes

Positive inotropic drugs, principally dobutamine or milrinone, have long been used to treat decompensated heart failure, despite the lack of data showing an outcome benefit to their use. In the past, some chronic heart failure patients would receive intermittent infusions of positive inotropic drugs as part of their maintenance therapy. Small studies consistently demonstrate improved hemodynamic values and reduced symptoms after administration of these agents to patients with heart failure. Studies comparing dobutamine to milrinone for advanced decompensated heart failure showed large differences in drug costs, favoring dobutamine, and only small hemodynamic differences, favoring milrinone.

Nevertheless, placebo-controlled studies suggest that there may be no role whatsoever for discretionary administration of positive inotropes to patients with chronic heart failure. In one study, 951 hospitalized patients with decompensated chronic heart failure who did not require intravenous inotropic support were assigned to receive a 48-hour infusion of either milrinone or saline. Meanwhile, all patients received ACE inhibitors and diuretics as deemed necessary. Total hospital days did not differ between groups; however, those receiving milrinone were significantly more likely to require intervention for hypotension or to have new atrial arrhythmias. A subanalysis of these results found that patients suffering from ischemic cardiomyopathy were particularly subject to adverse events from milrinone (a 42% incidence of death or rehospitalization versus 36% for placebo). At the present, positive inotropic drug support can be recommended only when there is no alternative. Thus, dobutamine and milrinone continue to be used to treat low CO in decompensated heart failure, but only in selected patients.[23]

Alternate Therapies

When drug treatment proves unsuccessful, heart failure patients may require invasive therapy, including ventricular assist devices, biventricular pacing, coronary artery bypass with or without surgical remodeling, or even cardiac orthotopic transplantation.

Low-Output Syndrome

Acute heart failure is a frequent concern of the cardiac anesthesiologist, particularly at the time of separation from cardiopulmonary bypass (CPB). The new onset of ventricular dysfunction and a low CO state after aortic clamping and reperfusion is a condition with more pathophysiologic similarity to cardiogenic shock than to

chronic heart failure and is typically treated with positive inotropic drugs, vasopressors (or vasodilators), if needed, and/or mechanical assistance. The latter more commonly takes the form of intra-aortic balloon counterpulsation and less commonly includes one of the several available ventricular assist devices.

Causes

Most patients undergoing cardiac surgery with CPB experience a temporary decline in ventricular function, with a recovery to normal function in a period of roughly 24 hours. Thus, pathophysiologic explanations must acknowledge the (usual) temporary nature of the low-output syndrome after CPB. Most likely, this results from one of three processes, all related to inadequate oxygen delivery to the myocardium: acute ischemia, hibernation, or stunning. All three processes would be expected to improve with adequate revascularization and moderate doses of positive inotropic drugs, consistent with the typical progress of the cardiac surgery patient. All three processes would be expected to be more troublesome in patients with preexisting chronic heart failure, pulmonary hypertension, or arrhythmias.

Risk Factors for the Low-Output Syndrome after Cardiopulmonary Bypass

The need for inotropic drug support after CPB can often be anticipated based on data available in the preoperative medical history, physical examination, and imaging studies. In a series of consecutive patients undergoing elective CABG, it was observed that increasing age, decreasing left ventricular ejection fraction, female sex, cardiac enlargement (on the chest radiograph), and prolonged duration of CPB were all associated with an increased likelihood that the patient would be receiving positive inotropic drugs on arrival in the intensive care unit. Similarly, in a study of patients undergoing cardiac valve surgery, it was found that increasing age, reduced left ventricular ejection fraction, and the presence of CAD all increased the likelihood that a patient would receive positive inotropic drug support.

Specific Drugs for Treating the Low-Output Syndrome

Whereas all positive inotropic drugs increase the strength of contraction in noninfarcted myocardium, mechanisms of action differ. These drugs can be divided into those that increase cyclic adenosine monophosphate (cAMP) (directly or indirectly) for their mechanisms of action and those that do not. The agents that do not depend on cAMP form a diverse group, including cardiac glycosides, calcium salts, calcium sensitizers, and thyroid hormone. In contrast to chronic heart failure, cardiac glycosides are not used for this indication, owing to their limited efficacy and narrow margin of safety. Calcium salts continue to be administered for ionized hypocalcemia and hyperkalemia, which are common occurrences during and after cardiac surgery. Increased Ca^{2+} in buffer solutions bathing cardiac muscle in vitro unquestionably increase inotropy. Calcium sensitizers, specifically levosimendan, function by binding to troponin C in a calcium-dependent fashion. Thus, levosimendan does not impair diastolic function because its affinity for troponin C declines with Ca^{2+} during diastole. Although several reports have described the successful use of levosimendan in patients recovering from CABG, clinical experience with this agent remains limited and there is no consensus as to how and when this agent should be used, relative to other, better established agents.[24]

Intravenous thyroid hormone (T_3, or liothyronine) has been studied extensively as a positive inotrope in cardiac surgery. There are multiple studies supporting the existence of euthyroid "sick" syndrome with persistent reduced concentrations of T_3 in blood after cardiac surgery in both children and adults. There are also data

suggesting that after ischemia and reperfusion, T_3 increases inotropy faster than and as potently as isoproterenol. Nevertheless, randomized controlled clinical trials have failed to show efficacy of T_3 after CABG.

The cAMP-dependent agents form the mainstays of positive inotropic drug therapy after cardiac surgery. There are two main classes of agents: the phosphodiesterase (PDE) inhibitors and the β-adrenergic receptor agonists. There are many different phosphodiesterase inhibitors in clinical use around the world, including enoximone, inamrinone, milrinone, olprinone, and piroximone. Comparisons among the agents have failed to demonstrate important hemodynamic differences. Reported differences relate to pharmacokinetics and rare side effects, typically observed with chronic oral administrations during clinical trials. All members of the class produce rapid increases in contractile function and CO and decreases in SVR. The effect on BP is variable, depending on the pretreatment state of hydration and hemodynamics; nevertheless, the typical response is a small decrease in BP. There is either no effect on HR or a small increase. Inamrinone and milrinone have been shown to be effective, first-line agents in patients with reduced preoperative left ventricular function. Milrinone, the most commonly used member of the class, is most often dosed at a 50-μg/kg loading dose and 0.5-μg/kg/min maintenance infusion. It is often given in combination with a β-adrenergic receptor agonist.

Among the many β-adrenergic receptor agonists, the agents most often given to patients recovering from cardiac surgery are dopamine, dobutamine, and epinephrine. Dopamine has long been assumed to have dose-defined receptor specificity. At small doses (0.5 to 3 μg/kg/min), it is assumed to have an effect mostly on dopaminergic receptors. At intermediate doses, β-adrenergic effects are said to predominate; and at doses of 10 μg/kg/min or greater, α-adrenergic receptor effects predominate. Nevertheless, the relationship between dose and blood concentration is poorly predictable. Dopamine is a relatively weak inotrope that has a predominant effect on HR rather than on SV.

Dobutamine is a selective β-adrenergic receptor agonist. Most studies suggest that it causes less tachycardia and hypotension than isoproterenol. It has been frequently compared with dopamine, where dobutamine's greater tendency for pulmonary and systemic vasodilation is evident. Dobutamine has a predominant effect on HR, compared with SV, and as the dose is increased more than 10 μg/kg/min there are further increases in HR without changes in SV.

Epinephrine is a powerful adrenergic agonist, and, like dopamine, demonstrates differing effects depending on the dose. At small doses (10 to 30 ng/kg/min), despite an almost pure β-adrenergic receptor stimulus, there is almost no increase in HR. Clinicians have long assumed that epinephrine increases HR more than dobutamine administered at comparable doses. Nevertheless, in patients recovering from cardiac surgery, the opposite is true: dobutamine increases HR more than epinephrine.

Other β-adrenergic agonists are used in specific circumstances. For example, isoproterenol is often used after cardiac transplantation to exploit its powerful chronotropy and after correction of congenital heart defects to exploit its pulmonary vasodilatory effects. Norepinephrine is exploited to counteract profound vasodilation.

Pharmacologic Treatment of Diastolic Heart Failure

Abnormal diastolic ventricular function is a common cause of clinical heart failure. As many as one in three patients presenting with clinical signs of chronic heart failure has a normal or near-normal ejection fraction (≥40%). The risk of diastolic heart failure increases with age, approaching 50% in patients older

than 70 years old. Diastolic heart failure is also more common in females and in patients with hypertension or diabetes mellitus. Although the prognosis of patients with diastolic heart failure is better than for systolic heart failure (5% to 8% vs. 10% to 15% annual mortality, respectively), the complication rate is the same. The 1-year readmission rate for patients with isolated diastolic heart failure approaches 50%.

In contrast to the large randomized trials that have led to the treatment guidelines for systolic heart failure, there are few randomized, double-blind, placebo-controlled, multicenter trials performed in patients with diastolic heart failure. Consequently, the guidelines are based on clinical experience, small clinical studies, and an understanding of the pathophysiologic mechanisms. The general approach to treating diastolic heart failure has three main components. First, treatment should reduce symptoms, primarily by lowering pulmonary venous pressure during rest and exercise by reducing left ventricular volume, maintaining AV synchrony, and increasing the duration of diastole by reducing HR. Second, treatment should target the underlying causes of diastolic heart failure. Specifically, ventricular remodeling should be reversed by controlling hypertension, replacing stenotic aortic valves, and treating ischemia. Third, treatment should target the underlying mechanisms that are altered by the disease processes, mainly neurohormonal activation. Drug treatment of diastolic heart failure with respect to these three goals is shown in Table 8-10.

Many of the drugs used to treat systolic heart failure are also used to treat diastolic heart failure. However, the reason for their use and the doses used may be different for diastolic heart failure. For instance, in diastolic heart failure β-blockers are used to increase the time of diastolic filling whereas in systolic heart failure, β-blockers are used to reverse heart remodeling (e.g., carvedilol). In fact, metoprolol-CR/XL may be a better β-blocker choice than carvedilol for diastolic heart failure because too low a BP (as a consequence of carvedilol) may be detrimental for the diastolic heart failure patient. Similarly, diuretic and NTG doses for diastolic heart failure are usually much smaller than for systolic heart failure, because the patient with diastolic heart failure is very sensitive to large reductions in preload. Calcium channel blockers are not a part of the armamentarium in the treatment of systolic heart failure but *may* be beneficial in treating diastolic heart failure through effects on rate control, specifically the long-acting dihydropyridine class of calcium channel blockers. With the exception of rate control in chronic atrial fibrillation, digoxin is not recommended for diastolic heart failure.

Except in the presence of acute diastolic heart failure, positive inotropic and chronotropic agents should be avoided because they may worsen diastolic function by increasing contractile force and HR, or by increasing calcium concentrations in diastole. However, in the short-term management of acute diastolic dysfunction or heart failure (e.g., post CPB), β-adrenergic agonists (e.g., epinephrine) and phosphodiesterase inhibitors (e.g., milrinone) enhance calcium sequestration by the sarcoplasmic reticulum and thereby promote a more rapid and complete myocardial relaxation between beats.[25,26]

Current Clinical Practice

The pharmacotherapy of heart failure begins with primary prevention of left ventricular dysfunction. Because hypertension and coronary artery disease are leading causes of left ventricular dysfunction, adequate treatment of both hypertension and hypercholesterolemia has been endorsed after encouraging results in prevention trials. Limitation of neurohormonal activation with ACE inhibitors, and possibly β-blockers, should be initiated in diabetic, hypertensive, and hypercholesterolemic

Table 8-10 Diastolic Heart Failure Treatments

Goal	Management Strategy	Drugs/Recommended Doses
Reduce the congestive state	Salt restriction Diuretics (avoid reductions in cardiac output) ACE inhibitors Angiotensin II receptor blockers	< 2 g of sodium/day Furosemide, 10 to 120 mg Hydrochlorothiazide, 12.5 to 25 mg Enalapril, 2.5 to 40 mg Lisinopril, 10 to 40 mg Candesartan, 4 to 32 mg Losartan, 25 to 100 mg
Target underlying cause Control hypertension Restore sinus rhythm Prevent tachycardia Prevent/treat ischemia Treat aortic stenosis	Antihypertensive agents (<130/80) Cardioversion of atrial fibrillation Atrioventricular sequential pacing β-Blockers, calcium channel blockers Morphine, nitrates, oxygen, aspirin Angioplasty or revascularization? Aortic valve replacement	β-Blockers, ACE inhibitors, all receptor blockers according to published guidelines Atenolol, 12.5 to 100 mg; metoprolol, 25 to 100 mg; diltiazem, 120 to 540 mg
Target underlying mechanisms Promote regression of hypertrophy and prevent myocardial fibrosis	(Theoretical) Renin-angiotensin axis blockade	Enalapril, 2.5 to 40 mg Lisinopril, 10 to 40 mg Captopril, 25 to 150 mg Candesartan, 4 to 32 mg Losartan, 50 to 100 mg Spironolactone, 25 to 75 mg Eplerenone, 25 to 50 mg

ACE = angiotensin-converting enzyme.
Adapted from Aurigemma GP, Gaasch WH: Clinical practice. Diastolic heart failure. N Engl J Med 351:1097, 2004.

patients (AHA/ACC, stage A heart failure) who are at increased risk for cardiovascular events, despite normal contractile function, in order to reduce the onset of new heart failure (HOPE trial). In patients with asymptomatic left ventricular dysfunction (ejection fraction = 40%) (stage B), treatment with ACE inhibitors and β-blockers can blunt the disease progression. In the symptomatic patient with heart failure (stage C), diuretics are titrated to relieve symptoms of pulmonary congestion and peripheral edema and achieve a euvolemic state whereas ACE inhibitors and β-blockers are recommended to blunt disease progression. Although digoxin has no effect on patient survival, it may be considered in stage C if the patient remains symptomatic despite adequate doses of ACE inhibitors and diuretics. In general, the primary treatment objectives for stages A to C heart failure are to (1) improve quality of life, (2) reduce morbidity, and (3) reduce mortality. At this time, the most important factor affecting long-term outcome is blunting of neurohormonal stimulation, because this mediates disease progression. Pharmacologic therapy in stage D, or patients with severe, decompensated heart failure, is based on hemodynamic status to alleviate symptoms with diuretics, vasodilators, and, in palliative circumstances, intravenous inotropic infusions. ACE inhibitors and β-blockers are

also incorporated in the treatment regimen to retard disease progression through reductions in ventricular enlargement, vascular hypertrophy, and ventricular arrhythmias[27] (Fig. 8-6).

PHARMACOTHERAPY FOR CARDIAC ARRHYTHMIAS

Perhaps the most widely used electrophysiologic and pharmacologic classification of antiarrhythmic drugs is that proposed by Vaughan Williams (Table 8-11). There is, however, substantial overlap in pharmacologic and electrophysiologic effects of specific agents among the classes, and the linkage between observed electrophysiologic effects and the clinical antiarrhythmic effect is often tenuous.[28]

Class I Antiarrhythmic Drugs: Sodium Channel Blockers

Class I drugs have the common property of inhibiting the fast inward depolarizing current carried by sodium ion. Because of the diversity of other effects of the class I drugs, a subgroup of the class has been proposed.

Class IA

PROCAINAMIDE

Electrophysiologic effects of procainamide include decreased Vmax and amplitude during phase 0, decreased rate of phase 4 depolarization, and prolonged effective refractory period (ERP) and action potential duration (APD). Clinically, procainamide prolongs conduction and increases the ERP in atrial and His-Purkinje portions of the conduction system, which may prolong PR interval and QRS complex durations.

Procainamide is used to treat ventricular arrhythmias and to suppress atrial premature beats to prevent the occurrence of atrial fibrillation and flutter. It has been very useful for chronic suppression of premature ventricular contractions.

Administered intravenously, procainamide is an effective emergency treatment for ventricular arrhythmias, especially after lidocaine failure, but, recently, amiodarone has become a more popular drug for intravenous suppression of ventricular arrhythmias.[29] Dosage is 100 mg, or approximately 1.5 mg/kg given at 5-minute intervals until the therapeutic effect is obtained or a total dose of 1 g or 15 mg/kg is given (Tables 8-12 and 8-13). Arterial pressure and the ECG should be monitored continuously during loading and administration stopped if significant hypotension occurs or if the QRS complex is prolonged by 50% or more. Maintenance infusion rates are 2 to 6 mg/min to maintain therapeutic plasma concentrations of 4 to 8 μg/mL.

Class IB

LIDOCAINE

First introduced as an antiarrhythmic drug in the 1950s, lidocaine has become the clinical standard for the acute intravenous treatment of ventricular arrhythmias except those precipitated by an abnormally prolonged QT interval. Lidocaine may, in fact, be one of the most useful drugs in clinical anesthesia because it has both local and general anesthetic properties, in addition to an antiarrhythmic effect.

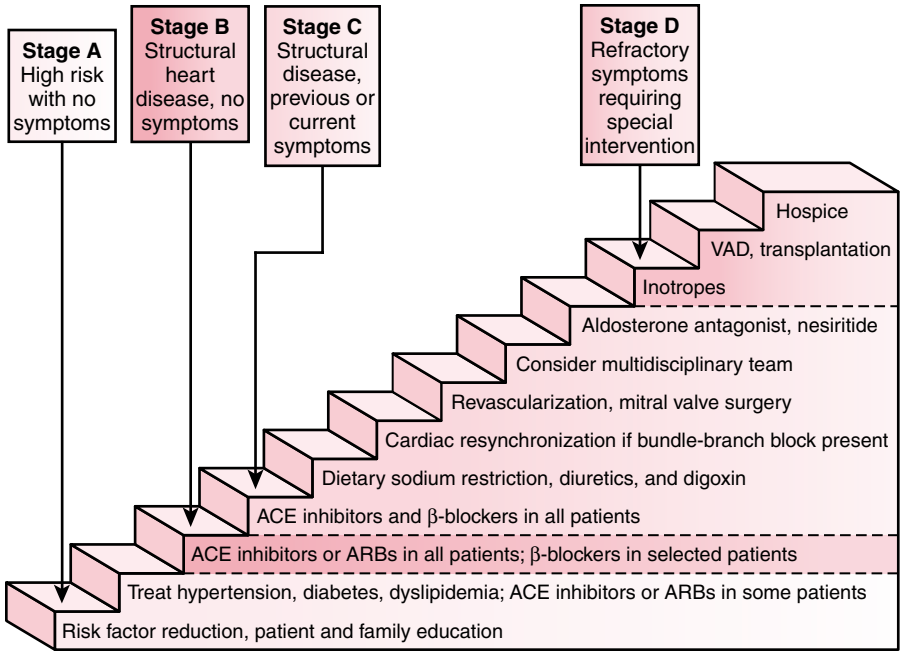

Figure 8-6 Treatment options for the stages of heart failure. (Redrawn from Jessup M, Brozena S: Heart failure. N Engl J Med 348:2007, 2003.)

Table 8-11 Classification of Antiarrhythmic Drugs

	Class			
Effect	*I (Membrane Stabilizers)*	*II (β-Adrenergic Receptor Antagonists)*	*III (Drugs Prolonging Repolarization)*	*IV (Calcium Antagonists)*
Pharmacologic	Fast channel (Na^+) blockade	β-Adrenergic receptor blockade	Uncertain: possible interference with Na^+ and Ca^{2+} exchange	Decreased slow-channel calcium conductance
Electrophysiologic	Decreased rate of Vmax	Decreased Vmax, increased APD, increased ERP, and increased ERP/APD ratio	Increased APD, increased ERP, increased ERP/APD ratio	Decreased slow-channel depolarization; decreased APD

Vmax = maximal rate of depolarization; APD = action potential duration; ERP = effective refractory period.

The direct electrophysiologic effects of lidocaine produce virtually all of its antiarrhythmic action. Lidocaine depresses the slope of phase 4 diastolic depolarization in Purkinje fibers and increases the ventricular fibrillation threshold. Lidocaine may be ineffective in hypokalemic patients.

Therapeutic plasma levels of lidocaine range from 1.5 to 5 μg/mL; signs of toxicity are frequent with concentrations above 9 μg/mL. An initial bolus dose of 1 to 1.5 mg/kg

Table 8-12 Intravenous Supraventricular Antiarrhythmic Therapy

Class I	Procainamide (IA)—converts acute atrial fibrillation, suppresses PACs and precipitation of atrial fibrillation/flutter, converts accessory pathway SVT. 100 mg IV loading dose every 5 min until arrhythmia subsides or total dose of 15 mg/kg (rarely needed) with continuous infusion of 2 to 6 mg/min.
Class II	Esmolol—converts or maintains slow ventricular response in acute atrial fibrillation. 0.5 to 1 mg/kg loading dose with each 50 μg/kg/min increase in infusion, with infusions of 50 to 300 μg/kg/min. Hypotension and bradycardia are limiting factors.
Class III	Amiodarone—converts acute atrial fibrillation to sinus rhythm; 5 mg/kg IV over 15 min. Ibutilide (Convert)—converts acute atrial fibrillation and flutter. Adults (>60 kg): 1 mg given over 10 min IV, may be repeated once. Adults (<60 kg) and children: 0.01 mg/kg given over 10 min IV, may be repeated once.
Class IV	Verapamil—slow ventricular response to acute atrial fibrillation, converts AV node reentry SVT. 75 to 150 μg/kg IV bolus. Diltiazem—slow ventricular response in acute atrial fibrillation, converts AV node reentry SVT. 0.25 μg/kg bolus, then 100 to 300 μg/kg/hr infusion.
Others	Adenosine—converts AV node reentry SVT and accessory pathway SVT. Aids in diagnosis of atrial fibrillation and flutter. Adults: 3 to 6 mg IV bolus, repeat with 6- to 12-mg bolus. Children: 100 μg/kg bolus, repeat with 200-μg/kg bolus. Increased dosage required with methylxanthines, decreased use required with dipyridamole. Digoxin—maintenance IV therapy for atrial fibrillation and flutter, slows ventricular response. Adults: 0.25-mg IV bolus followed by 0.125 mg every 1 to 2 hr until rate controlled, not to exceed 10 μg/kg in 24 hr. Children (<10 years of age): 10- to 30-μg/kg load given in divided doses over 24 hours. Maintenance: 25% of loading dose.

should be followed immediately by a continuous infusion of 20 to 50 μg/kg/min to prevent the "therapeutic hiatus" produced by the rapid redistribution half-life of lidocaine.[30]

Class II: β-Adrenergic Receptor Antagonists

β-Adrenergic receptor blockers are very effective antiarrhythmics in patients during the perioperative period or who are critically ill because many arrhythmias in these patients are adrenergically mediated.

Propranolol

Propranolol was the first major β-receptor–blocking drug to be used clinically. Propranolol is very potent but is nonselective for β_1/β_2-receptor subtypes.

The electrophysiologic effects of β-receptor antagonism are decreased automaticity, increased APD, primarily in ventricular muscle, and a substantially increased ERP in the AV node. β-Blockade decreases the rate of spontaneous (phase 4) depolarization in the SA node; the magnitude of this effect depends on the background sympathetic tone. Although resting HR is decreased by β-blockade, the inhibition of

Table 8-13 Intravenous Ventricular Antiarrhythmic Therapy

Class I	Procainamide (IA)—100 mg IV loading dose every 5 min until arrhythmia subsides or total dose of 15 mg/kg (rarely needed) with continuous infusion of 2 to 6 mg/min
	Lidocaine (IB)—1.5 mg/kg in divided doses given twice over 20 min with continuous infusion of 1 to 4 mg/min
Class II	Propranolol—0.5 to 1 mg given slowly up to a total β-blocking dose of 0.1 mg/kg. Repeat bolus as needed.
	Metoprolol—2.5 mg given slowly up to a total β-blocking dose of 0.2 mg/kg. Repeat bolus as needed.
	Esmolol—0.5 to 1.0 mg/kg loading dose with each 50 μg/kg /min increase in infusion, with infusions of 50 to 300 μg/kg/min. Hypotension and bradycardia are limiting factors.
Class III	Bretylium—5 mg/kg loading dose given slowly with a continuous infusion of 1 to 5 mg/min. Hypotension may be a limiting factor with infusion.
	Amiodarone—150 mg IV over 10 min, then 1 mg/min for 6 hours, then 0.5 mg/min for the next 18 hr. Repeat bolus as needed.
Others	Magnesium—2 g $MgSO_4$ over 5 min, then continuous infusion of 1 g/hr for 6 to 10 hr to restore intracellular magnesium levels.

Adapted from Management of Cardiac Rhythm Disturbances. *46th Annual Refresher Course Lectures and Clinical Update Program.* Park Ridge, IL: American Society of Anesthesiologists; 1995: No. 255.

the increase of HR in response to exercise or emotional stress is much more marked. Automaticity in the AV node and more distal portions of the conduction system is also depressed. β-Blockade affects the ventricular fibrillation threshold variably, but it consistently reverses the fibrillation threshold-lowering effect of catecholamines.

An appropriate intravenous dose for acute control of arrhythmias is 0.5 to 1.0 mg titrated to therapeutic effect up to a total of 0.1 to 0.15 mg/kg. Stable therapeutic plasma concentrations of propranolol can be obtained with a continuous intravenous infusion. An effective level of β-blockade may be obtained with a continuous infusion approximating 3 mg/hr in adult postoperative patients previously receiving chronic treatment; however, with the availability of esmolol, the need for a propranolol infusion is no longer necessary.

Esmolol

Esmolol is a cardioselective (β_1) receptor antagonist with an extremely brief duration of action. In anesthetized dogs, esmolol infused at 50 μg/kg/min produced a steady-state β-blockade that was completely reversed 20 minutes after stopping the infusion. Esmolol has no effect on LVEDP, BP, HR, CO, or SVR; however, at 5 to 60 μg/kg/min, it does decrease left ventricular dP/dt. The decreased contractility, however, fully resolves by 20 minutes after the infusion.

Esmolol is rapidly metabolized in blood by hydrolysis of its methyl ester linkage. Its half-life in whole blood is 12.5 and 27.1 minutes in dogs and humans, respectively. The acid metabolite possesses a slight degree (1500 times less than esmolol) of β-antagonism. Esmolol is not affected by plasma cholinesterase; the esterase responsible is located in erythrocytes and is not inhibited by cholinesterase inhibitors, but it is deactivated by sodium fluoride. Of importance to clinical anesthesia, no metabolic interactions between esmolol and other ester molecules

are known. Specifically, esmolol doses up to 500 μg/kg/min have not modified neuromuscular effects of succinylcholine.

Clinically, in asthmatic patients, esmolol (300 μg/kg/min) only slightly increases airway resistance. Also, in patients with chronic obstructive pulmonary disease who received esmolol, no adverse pulmonary effects occurred. In a multicenter trial, in a comparison with propranolol for the treatment of paroxysmal supraventricular tachycardia (PSVT), esmolol was equally efficacious and had the advantage of a much faster termination of the β-blockade. Esmolol has become a very useful agent in controlling sinus tachycardia in the perioperative period, a time when a titratable and brief β-blockade is highly desirable.

Dosing begins at 25 μg/kg/min and is titrated to effect up to 250 μg/kg/min. Doses higher than this may cause significant hypotension due to reduced CO in patients. Esmolol is especially effective in treating acute onset atrial fibrillation or flutter perioperatively and results in both acute control of the ventricular response and conversion of the arrhythmia back to sinus rhythm.[31]

Class III: Agents That Block Potassium Channels and Prolong Repolarization

Amiodarone

The drug has a wide spectrum of effectiveness, including supraventricular, ventricular, and preexcitation arrhythmias. It may also be effective against ventricular tachycardia and ventricular fibrillation refractory to other treatment. Amiodarone has been approved by the AHA as the first-line antiarrhythmic agent in cardiopulmonary resuscitation. Amiodarone may be effective prophylactically in preventing atrial fibrillation postoperatively. It also can decrease the number of shocks in patients who have implantable cardioverter defibrillators compared with other antiarrhythmic drugs.[32]

Amiodarone increases the amount of electric current required to elicit ventricular fibrillation (an increase in ventricular fibrillation threshold). In most patients, refractory ventricular tachycardia is suppressed by acute intravenous use of amiodarone. This effect has been attributed to a selectively increased activity in diseased tissue, as has been seen with lidocaine. Amiodarone also has an adrenergic-receptor (α and β) antagonistic effect produced by a noncompetitive mechanism; the contribution of this effect to the antiarrhythmic action of the drug is not known.

Hemodynamic effects of intravenously administered amiodarone include decreased left ventricular dP/dt, maximal negative dP/dt, mean aortic pressure, HR, and peak left ventricular pressure. A 5-mg/kg intravenous dose during cardiac catheterization decreased BP, LVEDP, and SVR and increased CO, but it did not affect HR. Chronic amiodarone therapy is not associated with clinically significant depression of ventricular function in patients without left ventricular failure. Hemodynamic deterioration may occur in some patients with compensated congestive heart failure, perhaps because of the antiadrenergic effects of the drug.

In acute situations with stable patients, a 150-mg intravenous bolus is followed by a 1.0-mg/min infusion for 6 hours and then 0.5 mg/min thereafter. In cardiopulmonary resuscitation, a 300-mg intravenous bolus is given and repeated with multiple boluses as needed if defibrillation is unsuccessful.

Despite relatively widespread use of amiodarone, anesthetic complications have infrequently been reported. In two case reports, bradycardia and hypotension were prominent. One of the reports described profound resistance to the vasoconstrictive effects of α-adrenergic agonists. The slow decay of amiodarone in plasma and tissue makes such adverse reactions possible long after discontinuing its administration. Because T_3 is reported

to reverse electrophysiologic effects of amiodarone, T_3 could possibly be used to reverse hemodynamic abnormalities, such as those described in these two case reports, although this theory has not been tested. Epinephrine has been shown to be more effective than dobutamine or isoproterenol in reversing amiodarone-induced cardiac depression.

Class IV: Calcium Channel Antagonists

Although the principal direct electrophysiologic effects of the three main chemical groups of calcium antagonists (verapamil, a benzoacetonitrite; nifedipine, a dihydropyridine; and diltiazem, a benzothiazepine) are similar, verapamil and diltiazem are the primary antiarrhythmic agents.

Verapamil and Diltiazem

Verapamil and diltiazem have been used extensively in the treatment of supraventricular arrhythmias, atrial fibrillation, and atrial flutter. They are especially effective at preventing or terminating PSVT by blocking impulse transmission through the AV node by prolonging AV nodal conduction and refractoriness. They are also useful in the treatment of atrial fibrillation and atrial flutter by slowing AV nodal conduction and decreasing the ventricular response. The effect on ventricular response is similar to that of the cardiac glycosides, although the onset is more rapid and acutely effective for control of tachycardia in patients.

In the perioperative period, verapamil is a useful antiarrhythmic agent. It successfully controlled a variety of supraventricular and ventricular arrhythmias. However, verapamil should be used cautiously intraoperatively because, in conjunction with inhalation anesthetics, significant cardiac depression may occur.

Verapamil dosage for acute intravenous treatment of PSVT is 0.07 to 0.15 mg/kg over 1 minute, with the same dose repeated after 30 minutes if the initial response is inadequate (10 mg maximum). Because the cardiovascular depressant effects of the inhalation anesthetics involve inhibition of calcium-related intracellular processes, the interaction of verapamil and these anesthetics is synergistic. In one large clinical series, verapamil given during steady-state halothane anesthesia transiently decreased BP and produced a 4% incidence of PR interval prolongation. In laboratory studies, verapamil interacts similarly with halothane, enflurane, and isoflurane to mildly depress ventricular function and to slow AV conduction (PR interval). AV block can occur, however, and may be refractory. In addition, AV block can occur when verapamil is combined with β-blockers.

Diltiazem in doses of 0.25 to 0.30 mg/kg administered intravenously followed by a titratable intravenous infusion of 10 to 20 mg/hr has been shown to be rapid acting and efficacious in controlling ventricular response rate in new-onset atrial fibrillation and atrial flutter. In addition, the prophylactic use of intravenous diltiazem has been shown to reduce the incidence of postoperative supraventricular arrhythmias after pneumonectomy and cardiac surgery. Diltiazem may also have a role in treating ventricular arrhythmias. In an experimental model, diltiazem has been shown to be protective against ventricular fibrillation with acute cocaine toxicity.

Other Antiarrhythmic Agents

Digoxin

The primary therapeutic use of digitalis drugs is to slow the ventricular response during atrial fibrillation or atrial flutter, which occurs because of a complex combination of direct and indirect actions on the AV node. The primary direct pharmacologic effect of digitalis is inhibition of the membrane-bound Na^+-K^+ ATPase.

The main preparation of cardiac glycosides available is digoxin. Digoxin reaches peak effects in 1.5 to 2 hours but has a significant effect within 5 to 30 minutes. For undigitalized patients, the initial dose is 0.5 to 0.75 mg of digoxin, with subsequent doses of 0.125 to 0.25 mg. The usual total digitalizing dose ranges from 0.75 to 1.0 mg by the intravenous route. Digoxin is approximately 25% protein bound, and the therapeutic range of plasma concentrations is 0.5 to 2.0 ng/mL.

Adenosine

The important cardiac electrophysiologic effects of adenosine are mediated by the A_1-receptor and consist of negative chronotropic, dromotropic, and inotropic actions. Adenosine decreases SA node activity, AV node conductivity, and ventricular automaticity. In many ways these effects mimic those of acetylcholine.

For clinical use, adenosine must be administered by a rapid intravenous bolus in a dose of 100 to 200 μg/kg, although continuous intravenous infusions of 150 to 300 μg/kg/min have been used to produce controlled hypotension. For practical purposes, in adults an intravenous dose of 3 to 6 mg is given by bolus followed by a second dose of 6 to 12 mg after 1 minute if the first dose was not effective. This therapy rapidly interrupts narrow-complex tachycardia caused by AV nodal reentry. Comparison with verapamil has shown adenosine to be equally effective as an antiarrhythmic agent but with the advantages of fewer adverse hemodynamic effects, a faster onset of action, and a more rapid elimination so that undesired effects are short-lived.[33]

Potassium

Because of the close relationship between extracellular pH and potassium, the primary mechanism of pH-induced arrhythmias may be alteration of potassium concentration. Both hypokalemia and hyperkalemia are associated with cardiac arrhythmias; however, hypokalemia is more common perioperatively in cardiac surgical patients and is more commonly associated with arrhythmias. Decreasing extracellular potassium concentration increases the peak negative diastolic potential, which would theoretically appear to decrease the likelihood of spontaneous depolarization. However, because the permeability of the myocardial cell membrane to potassium is directly related to extracellular potassium concentration, hypokalemia decreases cellular permeability to potassium. This prolongs the action potential by slowing repolarization, which in turn slows conduction and increases the dispersion of recovery of excitability and, thus, predisposes to the development of arrhythmias. ECG correlates of hypokalemia include appearance of a U wave and increased P-wave amplitude. The arrhythmias most commonly associated with hypokalemia are premature atrial contractions (PACs), atrial tachycardia, and supraventricular tachycardia (SVT). Hypokalemia also accentuates the toxicity of cardiac glycosides.

Moderate hyperkalemia, in contrast, increases membrane permeability to potassium, which increases the speed of repolarization and decreases APD, thereby decreasing the tendency to arrhythmias. An increased potassium concentration also affects pacemaker activity. The increased potassium permeability caused by hyperkalemia decreases the rate of spontaneous diastolic depolarization, which slows HR and, in the extreme case, can produce asystole. The repolarization abnormalities of hyperkalemia lead to the characteristic ECG findings of T-wave peaking, prolonged PR interval, decreased QRS amplitude, and a widened QRS complex. Both AV and intraventricular conduction abnormalities result from the slowed conduction and uneven repolarization.

Treatment of hyperkalemia is based on its magnitude and on the clinical presentation. For life-threatening, hyperkalemia-induced arrhythmias, the principle is rapid reduction of extracellular potassium concentration, a treatment that does not acutely decrease total body potassium content. Calcium chloride, 10 to 20 mg/kg, given by intravenous

infusion, will directly antagonize the effects of potassium on the cardiac cell membranes. Sodium bicarbonate, 1 to 2 mEq/kg, or a dose calculated from acid-base measurements to produce moderate alkalinity (pH approximately 7.45 to 7.50), will shift potassium intracellularly. A change in pH of 0.1 unit produces a 0.5 to 1.5 mEq/L change of potassium concentration in the opposite direction. An intravenous infusion of glucose and insulin has a similar effect; glucose at a dose of 0.5 to 2.0 g/kg with insulin in the ratio of 1 unit to 4 g of glucose is appropriate. Sequential measurement of serum potassium is important with this treatment because marked hypokalemia can result.

Acute hypokalemia frequently occurs after CPB as a result of hemodilution, urinary losses, and intracellular shifts, the latter perhaps relating to abnormalities of the glucose-insulin system seen with nonpulsatile hypothermic CPB. With frequent assessment of serum potassium concentrations and continuous ECG monitoring, potassium infusion at rates of up to 10 to 15 mEq/hr may be administered to treat serious hypokalemia.[34]

Magnesium

Magnesium deficiency is also a relatively common electrolyte abnormality in critically ill patients, especially in chronic situations. Hypomagnesemia is associated with a variety of cardiovascular disturbances, including arrhythmias. Sudden death from coronary artery disease, alcoholic cardiomyopathy, and congestive heart failure may involve magnesium deficiency. Functionally, magnesium is required for the membrane-bound Na^+/K^+ ATPase, which is the principal enzyme that maintains normal intracellular potassium concentration. Not surprisingly, the ECG findings seen with magnesium deficiency mimic those seen with hypokalemia: prolonged PR and QT intervals, increased QRS duration, and ST-segment abnormalities. In addition, as with hypokalemia, magnesium deficiency predisposes to the development of the arrhythmias produced by cardiac glycosides.

Arrhythmias induced by magnesium deficiency may be refractory to treatment with antiarrhythmic drugs and either electrical cardioversion or defibrillation. For this reason, adjunctive treatment of refractory arrhythmias with magnesium has been advocated even when magnesium deficiency has not been documented. Magnesium deficiency is common in cardiac surgery patients owing to the diuretic agents these patients are often receiving and because magnesium levels decrease with CPB because of hemodilution of the pump. Magnesium lacks a counterregulatory hormone to increase magnesium levels during CPB in contrast to the hypocalcemia that is corrected by parathyroid hormone. The results of magnesium administration trials involving CABG have been conflicting. Some studies have shown a benefit and others have not in regard to reducing the incidence of postoperative arrhythmias.[35]

SUMMARY

Anti-Ischemic Drug Therapy

- Ischemia during the perioperative period demands immediate attention by the anesthesiologist. The impact of ischemia may be both acute (impending infarction, hemodynamic compromise) and chronic (a marker of previously unknown cardiac disease, a prognostic indicator of poor outcome).
- Nitroglycerin is indicated in nearly all conditions of perioperative myocardial ischemia. Mechanisms of action include coronary vasodilation and favorable alterations in preload and afterload. Nitroglycerin is contraindicated when hypotension is present.

- Perioperative β-blockade may reduce the incidence of perioperative myocardial ischemia via a number of mechanisms. Favorable hemodynamic changes associated with β-blockade include a blunting of the stress response and reduced heart rate, blood pressure, and contractility. All of these conditions improve myocardial oxygen supply/demand ratios.
- Calcium channel blockers reduce myocardial oxygen demand by depression of contractility, heart rate, and/or decreased arterial blood pressure. Calcium channel blockers are often administered in the perioperative period for longer-term antianginal symptom control.

Drug Therapy for Systemic Hypertension

- Current guidelines suggest seeking a target blood pressure of less than 140/85 mm Hg to minimize long-term risk for adverse cardiovascular morbidity and mortality.
- For patients with diabetes, renal impairment, or established cardiovascular diseases, a lower target of less than 130/80 mm Hg is recommended.
- Mild-to-moderate hypertension does not represent an independent risk factor for perioperative complications; however, a diagnosis of hypertension necessitates preoperative assessment for target organ damage.
- Patients with poorly controlled preoperative hypertension experience more labile blood pressures in the perioperative setting with greater potential for hypertensive or hypotensive episodes or both.

Pharmacotherapy for Acute and Chronic Heart Failure

- The signs, symptoms, and treatment of chronic heart failure are as related to the neurohormonal response as they are to the underlying ventricular dysfunction.
- Current treatments of chronic heart failure are aimed at prolonging survival, not just relief of symptoms.
- The low cardiac output syndrome seen after cardiac surgery has a pathophysiology, treatment, and prognosis that differ from those of chronic heart failure, with which it is sometimes compared.

Pharmacotherapy for Cardiac Arrhythmias

- Physicians must be cautious in administering antiarrhythmic drugs because of the proarrhythmic effects that can increase mortality in certain subgroups of patients.
- Amiodarone has become a popular intravenous antiarrhythmic drug for use in the operating room and critical care areas because it has a broad range of effects for ventricular and supraventricular arrhythmias.
- β-Receptor antagonists are very effective but underused antiarrhythmic agents in the perioperative period because many arrhythmias are adrenergically mediated due to the stress of surgery and critical illness.
- Managing electrolyte abnormalities and treating underlying disease processes such as hypervolemia and myocardial ischemia are critical treatment steps before the administration of any antiarrhythmic agent.

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