

6 – Heart failure

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“There is but one meaning for the term cardiac failure—it signifies inability of the heart to discharge its contents adequately.”

Sir Thomas Lewis, 1933^[1]

“Management of [heart failure] can only grow as a concern for patients, doctors and health-system architects worldwide.”

Editorial, Lancet, 2011^[2]

“No single end point can capture all elements of the clinical course of acute heart failure syndromes, and therefore, no single end point will be appropriate for all interventions or patient populations.”

Felker GM, et al., 2010^[3]

Acute versus chronic heart failure

Heart failure is a clinical condition in which a functional or structural abnormality of the heart results in the common symptoms of exertional shortness of breath and tiredness. Despite this simple definition, establishing the presence and cause of heart failure is often challenging. Chronic heart failure is common (prevalence 1%-3% in populations, increasing with age to 10%), debilitating, detectable, treatable, and has a major economic effect on public health systems. The prognosis is poor depending on severity at the time of presentation; in the past up to 50% of treated patients were dead within 4 years. Current comprehensive therapy is improving the outlook. The two major causes in Western countries are hypertension and coronary artery disease (Fig. 6-1), with cardiomyopathy as another common cause in Africa. Lesser causes include genetic and familial abnormalities, and peripartum cardiomyopathy (PPCM) of hormonal-molecular causation has been recently recognized.

EVOLUTION OF HEART FAILURE

Opie 2012

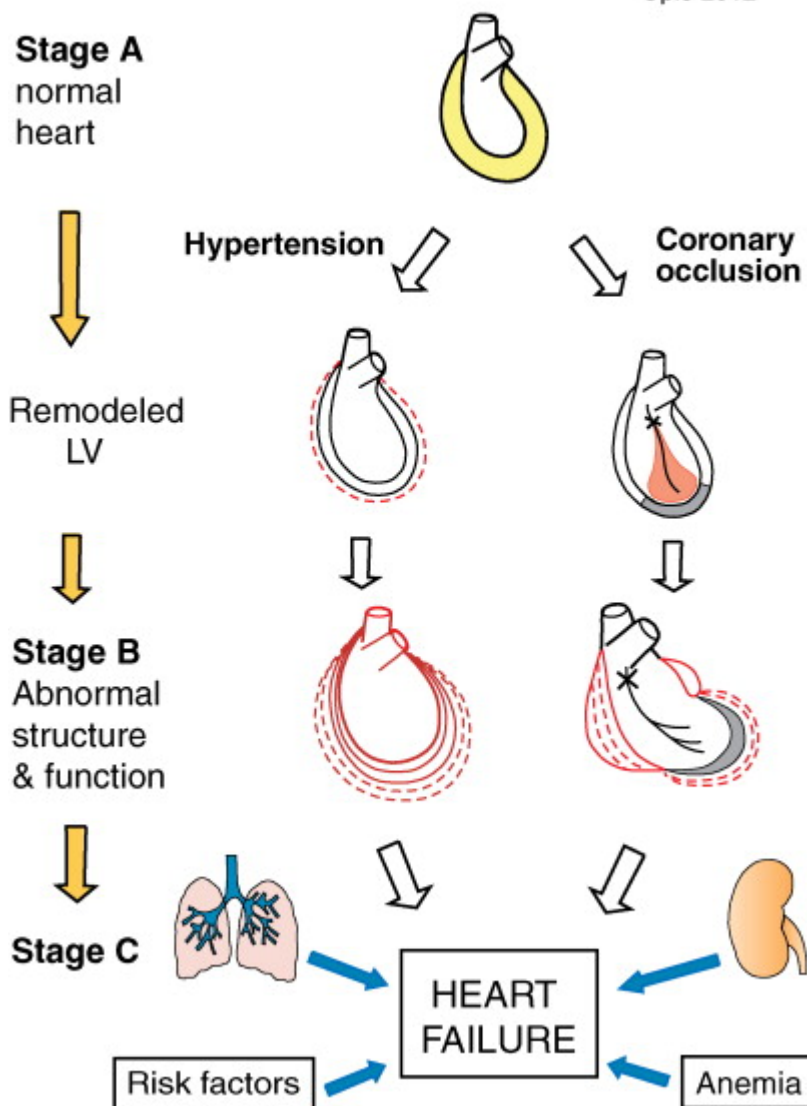


Figure 6-1 Evolution of heart failure. The two major routes to heart failure are, first, chronic hypertension and, second, coronary artery disease. Renal disease is one of the predisposing diseases, which include diabetes. Cardiomyopathy is more common in Africa. LV, Left ventricular. (Figure © L.H. Opie, 2012.)

Heart failure has been recognized and described for many centuries. As a consequence numerous words or phrases have become established in clinical practice. These include older terms such as *forward* and *backward failure*, *high* and *low output failure*, and *right* and *left heart failure*. More useful and current terminology includes *acute* and *chronic heart failure*, *systolic* (heart failure with reduced ejection fraction [HFrEF]; enlarged heart and reduced ejection fraction) and *diastolic* (heart failure with preserved ejection fraction [HFpEF]; near normal size heart or ejection fraction) *heart failure*, and adjectives such as *overt*, *treated*, *compensated*, *relapsing*, *congestive*, or *undulating*.

Two recognizable clinical categories are practically useful. (1) *Acute versus chronic heart failure*: Acute heart failure is characterized by the onset of severe symptoms, usually shortness of breath, requiring urgent or emergent treatment, and therapy is directed to the rapid improvement in these symptoms. Chronic heart failure may also be characterized by persistent but usually stable symptoms, and therapy has also been demonstrated to improve mortality and morbidity. Although there are cases of de novo acute heart failure, most cases of acute heart failure are decompensations of chronic heart failure. Whether acute and chronic

heart failure represent distinct pathophysiologic entities or are merely expressions of different severity is still debated, and beyond the scope of this chapter. (2) *Hypervolemic versus low output*: Most patients with heart failure present with signs and symptoms of volume overload, often including peripheral edema, rales, elevated central venous pressures, and dyspnea. Low-output heart failure, the extreme manifestation of which is cardiogenic shock, is recognized by peripheral constriction (cold peripheries, confusion, sweating), decreased end organ function (usually renal insufficiency with either anuria or oliguria), and a low systolic blood pressure (BP; less than 90 mm Hg). However, renal dysfunction may also be present in hypervolemic heart failure and should not be considered solely indicative of low output failure. Hypervolemic and low output heart failure are not mutually exclusive and may be present simultaneously, as well.

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Acute heart failure

In *acute heart failure* the symptom of shortness of breath is often related to high left atrial pressure. Treatment is aimed at immediate reduction of left atrial pressure (preload). Diuretics, nitrates, and possibly morphine (antianxiolytic) are used expeditiously. Intravenous natriuretic peptides (NPs; nesiritide) are now available, but their added benefit is questionable. Vasopressin is used in some acute situations for BP support and vasopressin antagonists, which reduce vasoconstriction and may aid diuresis, have been recently investigated.

Therapy of acute heart failure

A new classification of acute heart failure is (1) acute decompensated heart failure, dominated by fluid retention; and (2) acute vascular failure often caused by acute hypertension or other hemodynamic causes of acute pulmonary edema.^[4] Clinically, however, it is acute pulmonary edema and cardiogenic shock that must be urgently managed. Here the classification into dry-warm, wet-warm, dry-cold, and wet-cold (Table 6-1) provides prognostic information. “Wet” shock increases the risk of death by about twofold.^[5] Urgent clinical examination decides whether the dominant problem is a shocklike state with hypotension (dry shock), or acute pulmonary edema with acute dyspnea (wet shock), or both, the most serious. This complex situation often requires multiple drugs acting at various sites, depending on the overall hemodynamic status (Fig. 6-2). The major drug choices are shown in Table 6-2. The immediate treatment is upright sitting posture, oxygen, intravenous loop diuretics, and perhaps morphine with or without an antiemetic. However, the use of morphine has been questioned in the setting of acute coronary syndromes^[6] and acute heart failure,^[7] in which morphine was associated with worse clinical outcomes, even after adjustments for clinical and prognostic variables.

Table 6-1 -- Classification of Shock

		Congestion	
		—	+
Adequate Perfusion	+	Dry-warm	Wet-warm
	—	Dry-cold	Wet-cold

Based on Nohria A, et al. *J Am Coll Cardiol* 2003;41(10):1797–1804.

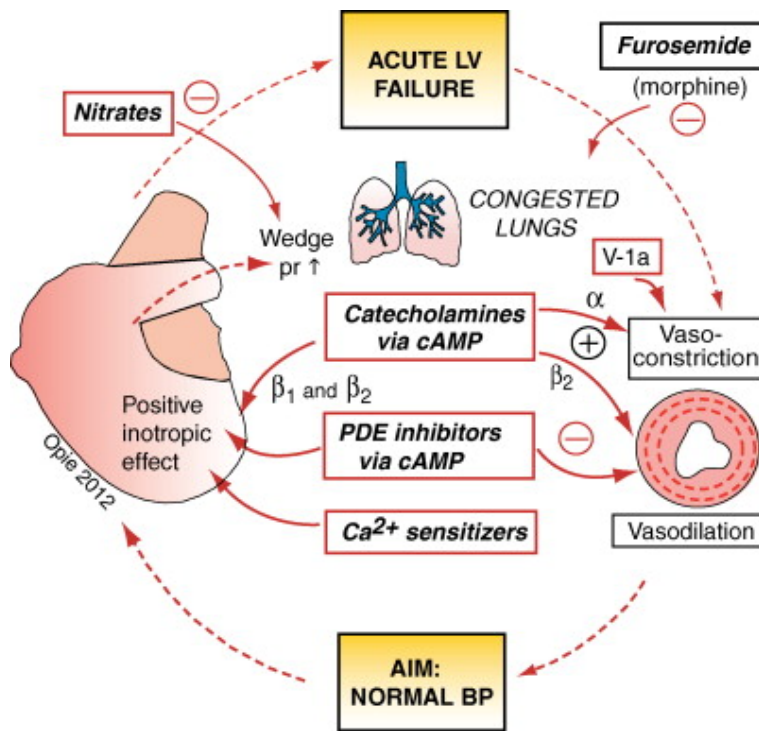


Figure 6-2 Sites of action of drugs used for acute left ventricular (LV) failure. Note opposing effects of (1) vasoconstriction resulting from α -adrenergic effects (norepinephrine, high doses of epinephrine or dopamine), and (2) vasodilation resulting from vascular cyclic adenosine monophosphate (cAMP) elevation from β_2 -effects or phosphodiesterase (PDE) inhibition (see Fig. 6-5). *alpha*, α -adrenergic; BP, blood pressure; pr, pressure; V-1a, vasopressin agonist acting on receptor subtype 1a. (Figure © L.H. Opie, 2012.)

Table 6-2 -- Drugs Used for Acute Heart Failure

<ol style="list-style-type: none"> Vasodilators—if signs of congestion and BP maintained, nitrates, sodium nitroprusside, nesiritide Diuretics—for fluid retention, with strategies against diuretic resistance (check electrolytes; combinations of diuretics; added dopamine; reduced ACE inhibitor dose); vasopressin-2 antagonist aquaretics for hyponatremia Inotropes—if peripheral hypoperfusion, dopamine, dobutamine, epinephrine, norepinephrine, levosimendan, phosphodiesterase inhibitors Vasopressin (AVP) for septic shock, CPR, intraoperative hypotension
Role of BP in drug choice:
<ol style="list-style-type: none"> Severe hypotension and shock: dopamine 5-20 mcg/kg/min or NE 0.5-30 mcg/min Modest hypotension: Vasodilator or inotrope (dobutamine or phosphodiesterase inhibitor or levosimendan) BP above 100 mm Hg: Nitroglycerin or nesiritide or BNP or nitroprusside
Role of sympathetic tone in acute heart failure:*
<ol style="list-style-type: none"> Tachycardia and atrial fibrillation. Paradoxical use of β-blockade when AHF is related to AF with rapid ventricular response: IV esmolol (see Table 8-2) Acute hypertension. IV esmolol may be used at higher dose than above (80 mg over 30 sec, then 150-300 mcg/min; see Chapter 1, p. 30)

ACE, Angiotensin-converting enzyme; AF, atrial fibrillation; AHF, acute heart failure; AVP, arginine vasopressin; BNP, B-type natriuretic peptide; BP, blood pressure; CPR, cardiopulmonary resuscitation; IV, intravenous; NE, norepinephrine.

*Data from Pang PS, et al. The current and future management of acute heart failure syndromes. *Eur Heart J* 2010;31:784–793.

Diuretics.

Given that the great majority of patients present with hypervolemia, intravenous diuretics are the most commonly administered therapy for acute heart failure. A small study of 304 patients used a factorial design to compare low versus high dose and bolus versus continuous furosemide infusion strategies, and suggested that patients treated with high-dose strategies (2.5× the previous oral dose) had a trend toward greater diuresis, improved symptoms, and transient worsening of renal function.^[8] Although there was no apparent short-term difference between the bolus compared with continuous infusion strategies, the attention of the clinical trial personnel and the regular frequency of the bolus dose administration may not be representative of a “real-world” clinical setting.

Diuretic dose and mortality.

There are no good randomized trials. Two studies using propensity matching with mortality as an outcome came to different conclusions. The ALARM-HF study recorded in-hospital heart failure therapy in 4953 patients receiving high- or low-dose intravenous furosemide if their total initial 24-hour dose was more than or less than 1 mg/kg.^[9] No association was found between diuretic dosing and death in any of the subgroups. In the second study, on 1354 patients with advanced systolic heart failure, patients were divided into quartiles of equivalent total daily loop diuretic dose. Even after extensive co-variate adjustment, there was a decrease in survival with increasing diuretic dose, 0-40 mg, 41-80 mg, 81-160 mg, and more than 160 mg (83%, 81%, 68%, and 53% for quartiles 1, 2, 3, and 4, respectively).^[10] Thus there are indirect arguments for both points of view; maybe a randomized trial will yet be done.

Worsening renal function.

In patients with acute heart failure, the high central venous pressure impairs renal function.^{[11],[12]} Urine output must be closely monitored. Diuretics, by relieving elevated central venous pressure, help preserve renal function.

Vasodilator therapy.

Vasodilator therapy is often coupled with diuretics in the treatment of choice for acute pulmonary edema. Sometimes the dyspnea is so severe that assisted ventilation is required. Abnormal vasoconstriction can be viewed as the central defect in many acute heart failure episodes.^{[13],[14]} Vasodilator treatment frequently achieves dramatic short-term benefits to save the patient from drowning in his or her own secretions, but is also useful in patients with less severe pulmonary congestion. It is likely that vasodilator therapy is underused, particularly in the United States. A small randomized trial of primarily nitrate therapy compared to a predominant diuretic approach in 110 patients with acute pulmonary edema and congestive heart failure (CHF) suggested clinical superiority of the vasodilator approach. Patients treated with *intravenous isosorbide dinitrate* had less need for mechanical ventilation and reduced frequency of myocardial infarction (MI).^[15] Interestingly, an analysis from the ALARM-HF registry suggested that patients treated with a combination of intravenous diuretics and vasodilators had lower in-hospital mortality than those patients treated solely with diuretics.^[16]

Sympathomimetic inotropes and inotropic dilators.

Sympathomimetic inotropes and inotropic dilators may provide some limited additional benefit in some patients with hypervolemic presentations, but are typically used for low cardiac output. There is little or no evidence that they provide long-term benefit, but rather, mortality may be increased (see “Milrinone” later in this chapter). Such drugs are best used as a means of temporarily supporting the failing heart, or as a bridge to a left ventricular (LV) assist device or transplantation. Inotropes or inodilators are indicated when the BP is low and renal perfusion is reduced. An important choice, largely depending on the BP and the peripheral perfusion, is whether to give an agent increasing or decreasing the peripheral vascular resistance by increasing or decreasing vasoconstriction, and whether to choose an inotropic agent or a vasodilator. Helpful algorithms are given in the European guidelines on the diagnosis and treatment of acute heart failure.^[17] Once acute intervention has stabilized the patient, the cause of the acute shocklike condition or the acute deterioration must be established. Thereafter the management is that of chronic heart failure.

Inotropic versus vasodilator therapy.

There are few outcome studies comparing inotropic versus vasodilator therapy in acute heart failure. In the ADHERE registry, a retrospective review of more than 65,000 patients suggested that mortality was lower with the vasodilators nitroglycerin or nesiritide than with dobutamine or milrinone.^[18] However, those treated by vasodilators had higher initial systolic BPs than those treated by inotropes, as might be expected. Corrections were made but this remains a posthoc observational study. A more statistically rigorous, although still posthoc, analysis was performed on more than 4000 patients from the ALARM-HF study using propensity-matching techniques. These analyses suggested that in-hospital mortality was increased 1.5-fold for dopamine or

dobutamine use and greater than 2.5-fold for norepinephrine or epinephrine use compared with patients treated solely with diuretics and vasodilators.^[16] Combinations of agents with different inotropic mechanisms or even vasodilators combined with positive inotropes were not considered in these analyses. The overall aims remain, first, maintaining an adequate but not excessive LV filling pressure ideally with cardiac output monitoring and, second, maintaining adequate urine flow.

Acute inotropes: Sympathomimetics and others

Physiologically, the basis of the acute inotropic response to an increased adrenergic drive is the rapid increase in the myocardial levels of the second messenger, cyclic adenosine monophosphate (cAMP; see Fig. 1-1). Pharmacologically, acute inotropic support uses the same principles, either by administration of exogenous catecholamines, which stimulate the β -receptor, or by inhibition of the breakdown of cAMP by phosphodiesterase (PDE) type III inhibitors (see Fig. 6-2). To give acute support to the failing circulation may require temporary peripheral vasoconstriction by β -adrenergic stimulation (Fig. 6-3). Hence there are a variety of catecholamine-like agents used for acute heart failure, depending on the combination of acute inotropic stimulation, acute vasodilation, and acute vasoconstriction that may be required (Table 6-3). Often the risk of arrhythmias must be balanced against the inotropic benefit. Countering pulmonary congestion and acute dyspnea requires intravenous furosemide and nitrates.

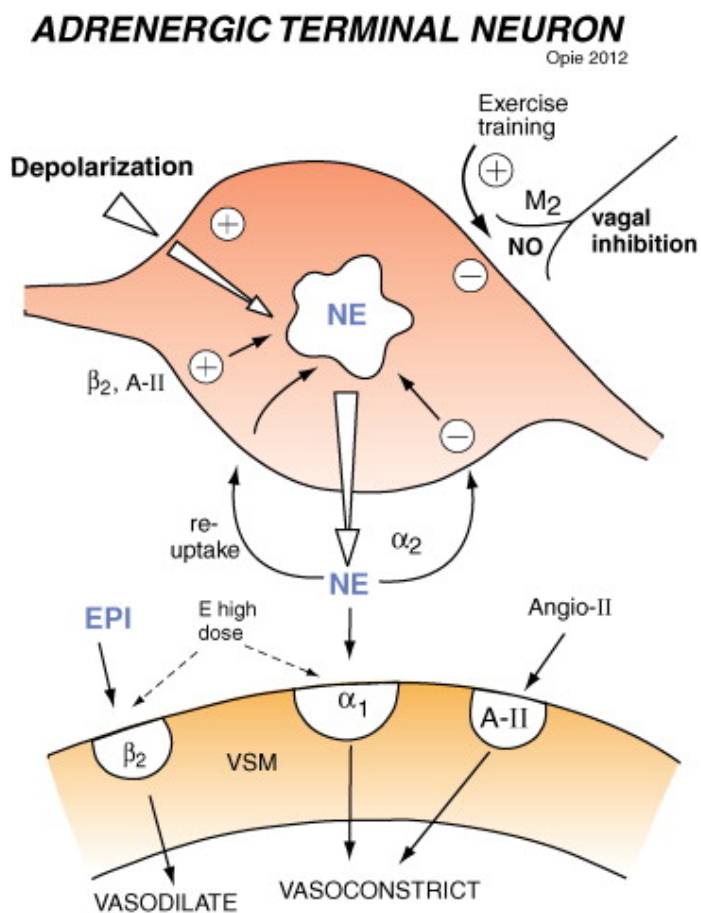


Figure 6-3 Role of adrenergic terminal neuron in regulation of vascular tone. Neuromodulation control of arteriolar constriction and dilation. *Upper panel*, terminal neuron; *lower panel*, vascular smooth muscle (VSM). Adrenergic sympathetic depolarization (*top left*) leads to release of norepinephrine (NE) from the storage granules of the terminal neurons into the synaptic cleft that separates the terminals from the arterial wall to act on postsynaptic vasoconstrictive β_1 -receptors. NE also stimulates presynaptic β_2 -receptors to invoke feedback inhibition of its own release, to modulate excess release of NE. By contrast, vagal cholinergic stimulation releases nitric oxide (NO), which acts on muscarinic receptors (subtype two, M2) to inhibit the release of NE, thereby indirectly causing vasodilation. Circulating epinephrine (EPI) stimulates vascular vasodilatory β_2 -receptors but also presynaptic receptors on the nerve terminal that promote release of NE. Angiotensin-II (A-II) formed in response to renin released from the kidneys in shocklike states is also powerfully vasoconstrictive, acting both by inhibition of NE release (presynaptic receptors, schematically shown to the *left* of the terminal neuron) and also directly on arteriolar receptors.

(Figure © L.H. Opie, 2012.)

Table 6-3 -- Sympathomimetic Inotropes for Acute Cardiac Failure Therapy

Drugs and Mediating Receptors	Dobutamine $\beta_1 > \beta_2 > \alpha$	Dopamine (Dopaminergic) $> \beta$; High Dose α)	Norepinephrine $\beta_1 > \alpha > \beta_2$	Epinephrine $\beta_1 = \beta_2 > \alpha$	Isoproterenol $\beta_1 > \beta_2$	Milrinone PDE inhibitor	Phenylephrine α -agonist
Dose infusion mcg/kg/min	2-15	2-5 renal effect 5-10 inotropic 10-20 SVR \uparrow	0.01-0.03max. 0.1	0.01-0.03max. 0.1-0.3	0.01-0.1	Bolus 50-75 (10 min) Drip 0.375-0.75	0.2-0.3
Elim $t_{1/2}$ minutes	2.4	2.0	3.0	2.0	2.0	150	20
Inotropic effect	$\uparrow\uparrow$	$\uparrow\uparrow$	\uparrow	$\uparrow\uparrow$	$\uparrow\uparrow\uparrow$	\uparrow	0
Arteriolar vasodilation	\uparrow	$\uparrow\uparrow$	0	\uparrow	\uparrow	$\uparrow\uparrow$	\downarrow
Vasoconstriction	HD \uparrow	HD $\uparrow\uparrow$	$\uparrow\uparrow$	HD \uparrow	0	0	$\uparrow\uparrow\uparrow$
Chronotropic effect	\uparrow	0, \uparrow	\uparrow	$\uparrow\uparrow$	$\uparrow\uparrow\uparrow$	0	0
Blood pressure effect	\uparrow	HD \uparrow	\uparrow	0, \uparrow	\uparrow	\downarrow	$\uparrow\uparrow\uparrow$
Diuretic effect (direct)	0	$\uparrow\uparrow$	\uparrow	0	0	0	\downarrow
Arrhythmia risk	$\uparrow\uparrow$	HD \uparrow	\uparrow	$\uparrow\uparrow\uparrow$	$\uparrow\uparrow\uparrow$	\uparrow	0

Elim $t_{1/2}$, Elimination half-life; HD, high dose; PDE, phosphodiesterase; SVR, systemic vascular resistance.

\uparrow , increase; 0, no change; \downarrow , decrease.

Cardiovascular therapeutic effects of adrenergic agents

Adrenergic effects on blood pressure.

In the case of norepinephrine, the net effect is BP elevation (dominant peripheral α -effects), whereas in the case of epinephrine at physiologic doses, the vasodilatory effects of β_2 -stimulation may offset the BP elevating effects of α -stimulation (see Fig. 6-2). The net effect of epinephrine is an elevation only of systolic BP (increased stroke volume) with a fall of diastolic BP (β_2 -peripheral dilation). Only at high pharmacologic doses of epinephrine does α -constriction elevate diastolic BP.

β -adrenergic stimulation of the acutely failing heart.

Sympathomimetic agents could thus benefit the acutely failing heart: β_1 -stimulation by an inotropic effect, β_2 -stimulation by afterload reduction (peripheral arterial vasodilation), and α -stimulation by restoring pressure in hypotensive states (see Table 6-2). Experimental work unfortunately shows that catecholamine stimulation, as exemplified by norepinephrine infusion, should be used with caution in the low-output state of acute myocardial infarction (AMI). β_1 -effects may precipitate arrhythmias and tachycardia, which can potentially increase ischemia, and promote cell death caused by metabolic exhaustion. Excessive α -effects increase the afterload as the BP rises beyond what is required for adequate perfusion, thus increasing myocardial work. Although β_2 -activation achieves beneficial vasodilation and also mediates some inotropic effect, such stimulation also causes hypokalemia with enhanced risk of arrhythmias. A further and serious problem is that prolonged or vigorous β_1 -stimulation may lead to or increase receptor downgrading with a diminished inotropic response (see Fig. 1-6). Catecholamine toxicity leads to myocyte breakdown and death. These are the reasons why sympathomimetics are used only in short-term treatment of acute heart failure.

In severe acutely decompensated chronic heart failure patients, those admitted on β -blockers, and also at discharge, had a decreased 180-day mortality.^[18A]

α -adrenergic effects.

If the BP is low, as in low-output heart failure, a crucial decision is whether it is desired to increase the BP solely by inotropic support or by a combination of inotropic and peripheral vasoconstrictory effects, or only by peripheral vasoconstriction. Although the latter aim can be achieved by pure α -stimulants, such as *phenylephrine* (5 to 20 mg in 500 mL slow infusion) or *methoxamine* (5 to 10 mg at 1 mg/min), this option is not logical, because heart failure automatically invokes reflex adrenergic vasoconstriction. Both these α -stimulants may nonetheless be useful in anesthetic hypotension.

Combined inotropic and vasoconstrictor effects.

Combined inotropic and vasoconstrictor effects are occasionally required, as may be achieved by high-dose dopamine. Furthermore, there are often defects in the rate of formation of cAMP in chronically failing hearts, such that a potentially useful combination becomes dopamine plus a PDE inhibitor such as milrinone. If only inotropic stimulation is required, dobutamine is the agent of choice, although there is the risk of mild decreases in the diastolic BP by its peripheral β_2 effect. If inotropic stimulation plus peripheral vasodilation is required, then dobutamine and a vasodilator, low-dose dopamine, or milrinone is appropriate.

Mixed adrenergic intravenous inotropes.

Mixed adrenergic intravenous inotropes ($\beta > \alpha$ -adrenergic stimulation) have as their common property the stimulation of both β - and α -adrenergic receptors to a varying degree. α -adrenergic stimulation also results in some modest positive inotropic response in the human heart, probably of greater importance when α -receptors are relatively upgraded as in severe CHF. Included in this group of mixed adrenergic agents is dobutamine, previously considered as highly selective for β_1 -receptors, but now thought also to stimulate β_2 and α -receptors (see Table 6-2).

Dobutamine

Dobutamine, a synthetic analog of dopamine, is a competitive β -adrenergic stimulating agent ($\beta_1 > \beta_2 > \alpha$). Its major characteristic is a potent inotropic effect (Fig. 6-4). However, its β_2 stimulatory effect may lead to hypotension and sometimes to a fall in diastolic pressure with reflex tachycardia. Furthermore, long-term mortality may be increased,^[19] as well as increasing cardiac sympathetic activity in heart failure patients

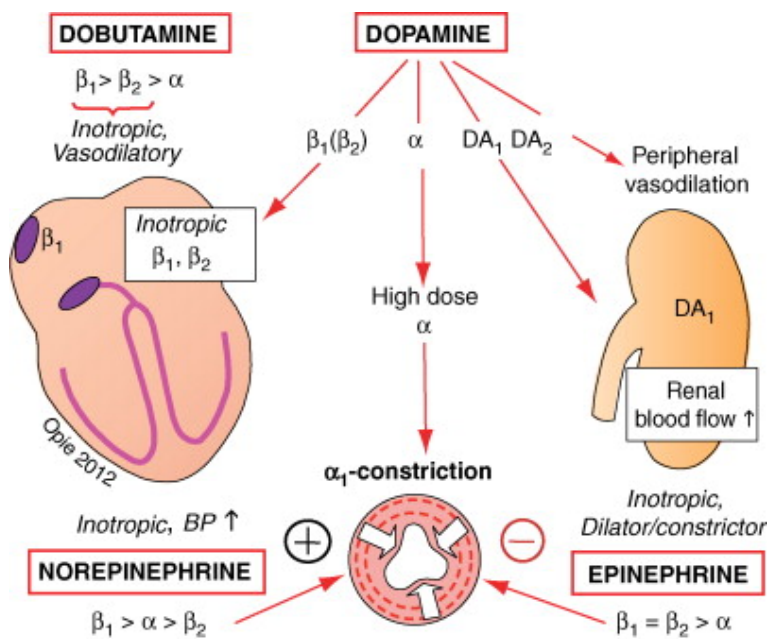


Figure 6-4 Catecholamine therapy. Receptor-specific effects of physiologic and pharmacologic agents. BP, Blood pressure; DA, dopaminergic. (Figure © L.H. Opie, 2012.)

Pharmacokinetics, dose, and indications.

An infusion is rapidly cleared (half-life 2.4 minutes). The standard intravenous dose is 2.5 to 10 mcg/kg/min, with

lower doses (2.5-5 mcg/kg/min) frequently sufficient, and rarely up to 40 mcg/kg/min. The drug can be infused for up to 72 hours with monitoring. There is no oral preparation. *Indications* are acute-on-chronic refractory heart failure, severe AMI (after cardiac surgery), cardiogenic shock, and excess β -blockade.

Dobutamine use, side effects, and precautions.

The ideal candidate for dobutamine therapy is the patient who has severely depressed LV function with a low cardiac index and elevated LV filling pressure, but in whom extreme hypotension is not present (mean arterial BP < 70 mm Hg but no clinical shock). Currently a major use of dobutamine is in *stress echocardiography*. The potential disadvantages of dobutamine are that (1) in severe CHF the β -receptors may be downgraded or therapeutically blocked so that dobutamine may not be as effective as anticipated,^[20] (2) BP may decrease or stay unchanged and not increase, and (3) sinus tachycardia or other more serious arrhythmias may occur.^[19] Although there are less arrhythmias and tachycardia than with isoproterenol, all inotropic agents increasing cytosolic calcium have the risk of enhanced arrhythmias. Tolerance to the inotropic effect may develop after prolonged infusion. A *precaution* is to dilute in sterile water or dextrose or saline, not in alkaline solutions. Use within 24 hours. Hemodynamic or careful clinical monitoring of the patient is required. Check blood potassium to minimize arrhythmias.

Dopamine

Dopamine is a catecholamine-like agent used for therapy of severe heart failure and cardiogenic shock. Physiologically, it is both the precursor of norepinephrine and releases norepinephrine from the stores in the nerve-endings in the heart (see Fig. 6-4). However, in the periphery this effect is overridden by the activity of the prejunctional dopaminergic-2 receptors, inhibiting norepinephrine release and thereby helping to vasodilate. Therefore overall dopamine stimulates the heart by both β - and α -adrenergic responses and causes vasodilation through dopamine receptors. Theoretically, dopamine has the valuable property in severe CHF or shock of specifically increasing blood flow to the renal, mesenteric, coronary, and cerebral beds by activating the specific postjunctional dopamine DA₁-receptors, although clinical data conflict on the utility of this effect.^[21] At high doses dopamine causes α -receptor stimulation with peripheral vasoconstriction; the peripheral resistance increases and renal blood flow falls. The dose should therefore be kept as low as possible to achieve the desired ends.

Properties and use of dopamine.

Dopamine, a "flexible molecule," also fits into many receptors to cause direct β_1 - and β_2 -receptor stimulation, as well as α -stimulation. The latter explains why in high doses dopamine causes significant vasoconstriction. *Pharmacokinetics:* Dopamine is inactive orally. Intravenous dopamine is metabolized within minutes by dopamine β -hydroxylase and monoamine oxidase (MAO).

Dose and indications.

Dopamine can only be given intravenously, which restricts its use to short-term treatment. The dose starts at 0.5 to 1 mcg/kg/min and is increased until an acceptable urinary flow, BP, or heart rate is achieved; vasoconstriction begins at approximately 10 mcg/kg/min and becomes marked at higher doses, occasionally necessitating the addition of an α -blocking agent or sodium nitroprusside. In a few patients vasoconstriction can begin at doses as low as 5 mcg/kg/min. In cardiogenic shock or AMI, 5 mcg/kg/min of dopamine is enough to give a maximum increase in stroke volume, whereas renal flow reaches a peak at 7.5 mcg/kg/min, and arrhythmias may appear at 10 mcg/kg/min. In septic shock, dopamine has an inotropic effect and increases urine volume. Dopamine is widely used after cardiac surgery. Worsening renal function and hypokalemia related to diuretic use for acute decompensated heart failure are common and associated with poor prognosis. Low-dose dopamine infusion improves renal perfusion.

Combination with furosemide.

In acute heart failure patients, the combination of low-dose furosemide (5 mg/h) and low-dose dopamine (5 mcg/kg/min) as a continuous infusion for 8 hours was equally effective as high-dose furosemide but associated with improved renal function profile and potassium homeostasis.^[22]

"Renoprotective" doses.

Dopamine is sometimes given for renal protection or for diuresis in critically ill patients at a typical dose of 0.5 to 2.5 mcg/kg/min. This dose did not work in an intensive care setting, arguing against the renoprotective concept.^[21] However, in a carefully titrated dose-response study using intravascular ultrasound in patients with severe chronic heart failure, a dose of 3-5 mcg/kg/min increased renal blood flow, and the higher dose increased cardiac output.^[23] This study reinstates the "renal dose" and forms the basis for other ongoing studies. In critically ill

hypoxic patients, dopamine may have undesirable side effects such as depression of ventilation and increased pulmonary shunting, which may require supplemental oxygen.^[24] "Renal dose" dopamine has not been demonstrated to prevent *contrast-dye nephropathy*,^[25] and *intermittent outpatient dopamine* for chronic heart failure does not work^[26] and may do harm.

Precautions, side effects, and interactions.

Dopamine must not be diluted in alkaline solutions. BP, electrocardiogram, and urinary flow are monitored constantly with intermittent measurements of cardiac output and pulmonary wedge pressure if possible. For oliguria, first correct hypovolemia; try furosemide. Dopamine is contraindicated in ventricular arrhythmias, and in pheochromocytoma. Use with care in aortic stenosis. Extravasation can cause sloughing, prevented by infusing the drug into a large vein through a plastic catheter, and treated by local infiltration with phentolamine. If the patient has recently taken a MAO inhibitor, the rate of dopamine metabolism by the tissue will fall and *the dose should be cut to one tenth* of the usual.

Comparison of dopamine and dobutamine.

Dopamine is the preferred inotrope in the patient who requires both a pressor effect (high-dose α -effect) and increase in cardiac output, and who does not have marked tachycardia or ventricular irritability. In cardiogenic shock, infusion of equal concentrations of dopamine and dobutamine may afford more advantages than either drug singly. The key to the effective use of these (and all intravenous inotropes) is careful monitoring of the clinical and hemodynamic response in the individual patient.

Epinephrine (adrenaline)

Epinephrine gives mixed β_1 - and β_2 -stimulation with some added α -mediated effects at a high dose (see Table 6-2). A low physiologic infusion rate (<0.01 mcg/kg/min) decreases BP (vasodilator effect), whereas more than 0.2 mcg/kg/min increases peripheral resistance and BP (combined inotropic and vasoconstrictor effects). It is used chiefly when combined inotropic-chronotropic stimulation is urgently needed, as in cardiac arrest (see Fig. 12-10), in which the added α -stimulatory effect of high-dose epinephrine helps maintain the BP and overcomes the peripheral vasodilation achieved by β_2 -receptor stimulation. The acute *dose* is 0.5 mg subcutaneously or intramuscularly (0.5 mL of 1 in 1000), or 0.5 to 1 mg into the central veins, or 0.1 to 0.2 mg intracardiac. The *terminal half-life* is 2 minutes. *Side effects* include tachycardia, arrhythmias, anxiety, headaches, cold extremities, cerebral hemorrhage and pulmonary edema. *Contraindications* include late pregnancy because of risk of inducing uterine contractions.

Use in septic shock.

In 330 mechanically ventilated patients with septic shock and a mean arterial BP of 70 mm Hg, epinephrine 0.2 mcg/kg/min gave similar outcome and mortality results to norepinephrine 0.2 mcg/kg/min plus dobutamine 5 mcg/kg/min.^[27] However, as there was no placebo group, epinephrine could have caused as much harm (or benefit) as norepinephrine plus dobutamine.

Norepinephrine (noradrenaline)

Norepinephrine is given in an *intravenous dose* of 8 to 12 mcg/min with a terminal half-life of 3 minutes. This catecholamine has prominent β_1 - and α -effects with less β_2 -stimulation. Norepinephrine chiefly stimulates α -receptors in the periphery (with more marked α -effects than epinephrine) and β -receptors in the heart. Logically, norepinephrine should be of most use when a shocklike state is accompanied by peripheral vasodilation ("*warm shock*"). In the future, drugs inhibiting the formation of vasodilatory nitric oxide (NO) will probably be of greater use in such patients. *Side effects* of norepinephrine include headache, tachycardia, bradycardia, and hypertension. As with all of the catecholamines and vasodilators, note the risk of necrosis with extravasation. *Combination therapy* with PDE inhibitors helps to avoid the hypotensive effects of the PDE inhibitors. *Contraindications* include late pregnancy (see "Epinephrine" earlier in chapter) and preexisting excess vasoconstriction.

Isoproterenol (isoprenaline)

This relatively pure β -stimulant ($\beta_1 > \beta_2$) is still sometimes used. Its cardiovascular effects closely resemble those of exercise, including a positive inotropic and vasodilatory effect. Theoretically, it is most suited to situations in which the myocardium is poorly contractile and the heart rate slow, yet the peripheral resistance high as, for example, after cardiac surgery in patients with prior β -blockade. Another ideal use is in β -blocker overdose. The intravenous dose is 0.5 to 10 mcg/min, the plasma half-life is approximately 2 minutes, and the major problem lies in the risk of tachycardia and arrhythmias. Furthermore, it may drop the diastolic BP by its β_2 -vasodilator stimulation. Other side effects are headache, tremor, and sweating. Contraindications include myocardial ischemia,

which can be exacerbated, and arrhythmias.

β_2 -agonists

In healthy volunteers, β_2 -receptors mediate chronotropic, inotropic, and vasodilator responses. Although not well tested in CHF in which there is known cardiac β_2 -receptor uncoupling, some evidence suggests clinical benefit in patients already treated by diuretics and digoxin. The drugs used are basically bronchodilators (terbutaline; albuterol = salbutamol) and should therefore theoretically be ideal for the combination of chronic obstructive airways disease and CHF. By inducing hypokalemia and prolonging the QT-interval, β_2 -agonists may increase the risk of arrhythmias. The pharmacologic characteristics of some of the newer β_2 agonists are complex. *Clenbuterol* has been used in patients on LV assist devices and any advantage may be attributable to hemodynamic effects or to metabolic actions.

Calcium sensitizers

When using calcium sensitizers the principle is that there is no attempt to increase cell calcium, the common mechanism of action of the conventional inotropes with the inevitable risk of arrhythmias. Rather the contractile apparatus is sensitized to the prevailing level of calcium. Theoretically these agents should increase contractile force without the risk of calcium-induced arrhythmias. This expectation has not been met in the case of several members of this group that also have PDE inhibitory properties with arrhythmogenic risks. *Levosimendan* is licensed in some European countries but not in the United States. It sensitizes troponin C to calcium, without impairing diastolic relaxation.^[28] In addition, it has vasodilatory effects mediated by opening of vascular adenosine triphosphate-sensitive potassium channels.^[28] Vasodilation, which may promote reflex tachycardia, may also result from PDE 3 inhibition. In the LIDO study of 103 patients in severe low-output heart failure, levosimendan (infused at 0.1 mcg/kg/min for 24 hours after a loading dose of 24 mcg/kg over 10 min) compared well with dobutamine (5-10 mcg/kg/min) in that hemodynamic improvement was accompanied by reduced mortality up to 180 days.^[28] No placebo group was included so that the difference could have been caused by harmful effects of dobutamine. In SURVIVE, in acute decompensated heart failure in 1327 patients, levosimendan had a similar primary outcome (all-cause mortality at 180 days) to dobutamine.^[29] Levosimendan was better at reducing heart failure (quicker early fall in plasma B-type natriuretic peptide [BNP], less heart failure at 180 days) at the cost of more atrial fibrillation and hypokalemia. In the REVIVE II trial, patients treated with levosimendan had shorter hospital length of stay and lower cost for the initial hospital admission relative to patients treated with standard of care.^[30] Based on subgroup analysis of patients administered per the current label, levosimendan appears cost-effective relative to standard of care.

Agents with both inotropic and vasodilator properties

Although *inodilation* is a term coined by Opie in 1986,^[31] the rationale goes back at least to 1978 when Stemple et al.^[32] combined the advantages of the vasodilator effects of nitroprusside with the inotropic effect of dopamine, thereby reducing both afterload and preload. Strictly speaking, dobutamine and low-dose dopamine should also be included as inodilators. Nonetheless, it is the PDE type III inhibitors that are the prototypical agents (Fig. 6-5). As a group, the inodilators have not improved mortality or morbidity in trials, and their use should be reserved for very serious hemodynamic situations such as LV failure with an inadequate low cardiac output despite adequate LV filling pressure.^[33]

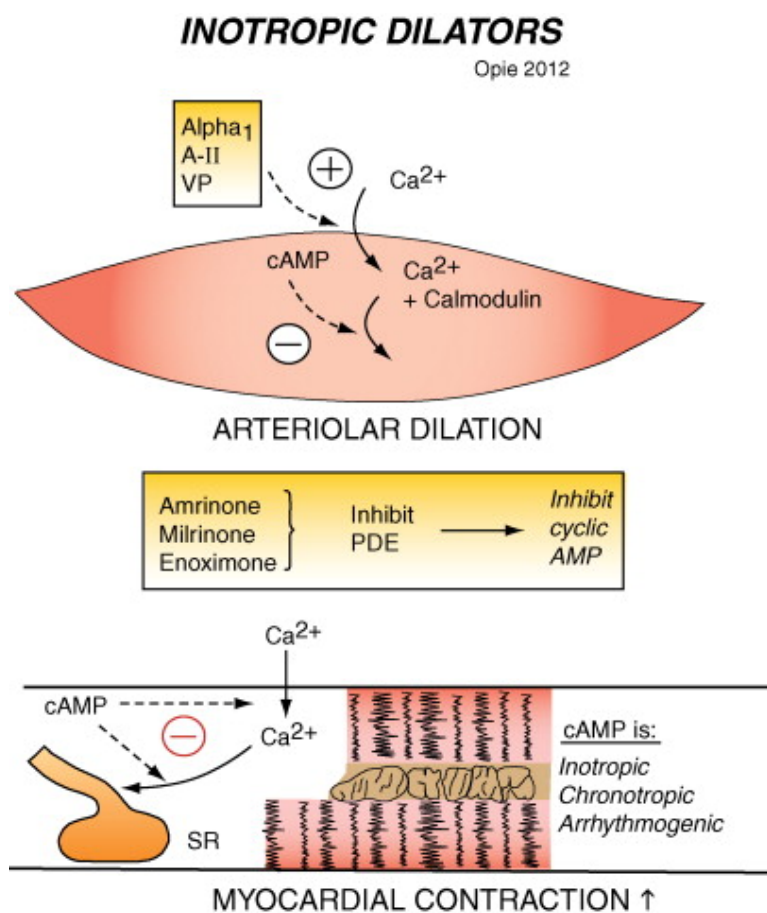


Figure 6-5 Inotropic dilators (“inodilators”) have as their mechanism of action an increase of cyclic adenosine monophosphate in vascular smooth muscle (*top*) and in myocardium (*bottom*). *Alpha1*, alpha1-adrenergic stimulation; *A-II*, Angiotensin-II; *PDE*, phosphodiesterase; *SR*, Sarcoplasmic reticulum; *VP*, vasopressin. (Figure © L.H. Opie, 2012.)

Phosphodiesterase type III inhibitors

PDE type III inhibitors, epitomized by milrinone, inhibit the breakdown of cAMP in cardiac and peripheral vascular smooth muscle, resulting in augmented myocardial contractility and peripheral arterial and venous vasodilation (see Fig. 6-5). Milrinone can substantially increase heart rate and decrease BP. The added dilator component may explain relative conservation of the myocardial oxygen consumption. Nonetheless, the increased levels of myocardial cAMP predispose to atrial and ventricular arrhythmias, which could explain the findings in the Milrinone-Digoxin trial in which milrinone was no better than digoxin and led to an increase in ventricular arrhythmias.^[34] The only inotropic dilator currently licensed in the United States is milrinone, although both milrinone and enoximone are available in the United Kingdom.

Milrinone.

Milrinone is approved for intravenous use in the United States and United Kingdom. Its pharmacologic mechanism of action is by PDE type III inhibition. The package insert gives a prominent warning that there is no evidence for efficacy or safety when given for longer than 48 hours. The further warning is that long-term oral use increased ventricular arrhythmias^[34] and mortality.^[35] In the large OPTIME-CHF trial on 949 patients with acute exacerbations of heart failure on a background of chronic heart failure, milrinone gave no additional benefit beyond placebo, yet caused more complications such as new atrial fibrillation and sustained hypotension without any overall mortality benefit.^[36] A later analysis revealed a trend of worse outcomes in the outcome benefit in the ischemic patients.^[37] There is no evidence that long-term continuous or intermittent infusion imparts benefit without potentially serious hazards.

Indications and doses are as follows. Milrinone is licensed only for intravenous use in patients with low output heart failure who are closely monitored, with facilities to treat any acute life-threatening ventricular arrhythmias that

may arise. There is no clinical trial experience with infusions longer than 48 hours. A slow intravenous loading dose (over 10 minutes, diluted before use, 50 mcg/kg) may be used, although many clinicians omit the initial load to avoid hypotensive effects, followed by an intravenous infusion at a rate of 0.375 to 0.750 mcg/kg/min, usually for up to 12 hours following surgery or up to 48 hours in acute heart failure; the maximum daily dose is 1.13 mg/kg. Reduce the dose in renal failure according to the creatinine clearance (see package insert). For example, a clearance of 20 mL/min/1.73 m² gives an infusion rate of 0.28 mcg/kg/min. *Contraindications* are AMI, severe aortic stenosis, or hypertrophic obstructive subaortic stenosis. *Short-term inotropic support* by milrinone on top of the otherwise optimal management of exacerbations of chronic heart failure cannot be recommended unless there is clear clinical need for inotropes or pressor agents.

Combination therapy and drug interactions are as follows. Milrinone gives added hemodynamic benefit to patients already receiving angiotensin-converting enzyme (ACE) inhibitors, with, however, a high risk of vasodilatory side effects. Milrinone may be combined with modest doses of dobutamine, enhancing the inotropic effects and lowering filling pressures. When the BP is low, milrinone may be combined with high-dose dopamine. Other than increased tachycardia and arrhythmias, there appear to be few or no adverse drug interactions.

Enoximone.

Enoximone is an investigational agent not available in the United States that is licensed for intravenous use in the United Kingdom (loading dose: 90 mcg/kg/min over 10 to 30 minutes, then 5-20 mcg/kg/min, decrease doses in renal failure). Although licensed for CHF in cases in which cardiac output is reduced and filling pressures increase, in practice it should ideally be used for acute, not chronic, heart failure or in bridging situations such as for patients awaiting transplantation. It seems that enoximone has not overcome the common problem of PDE inhibitors, namely enhancement of cAMP levels with a consequent risk of serious arrhythmias. The latter might explain why enoximone increased mortality in severe heart failure, whereas the central stimulatory effects of cAMP might explain why physical mobility and quality of life improved.^[38] This unexpected paradox triggered a debate, not yet resolved, about whether it is more important to improve the quality or quantity of life in chronic, severe, end-stage heart failure.

Novel approaches to increasing cardiac performance

As noted previously, all of the currently available inotropes and inodilators operate via a mechanism that increases intracellular cAMP and calcium with resultant increases in heart rate and myocardial oxygen demand with consequent increases in ischemia, arrhythmias, and death. Multiple new approaches have been developed to improve cardiac performance potentially without these liabilities. One promising approach includes the direct activation of cardiac myosin, and two human studies report the effects of the cardiac myosin activator, omecamtiv mecarbil, in volunteers or in patients with systolic heart failure. The first-in-man (34 healthy men) study showed highly dose-dependent increased LV systolic function in response to intravenous omecamtiv mecarbil and supported potential clinical use of the drug in patients with heart failure.^[39]

In an associated article on 45 patients with stable guideline-treated systolic heart failure, intravenous omecamtiv mecarbil gave concentration-dependent increases in LV ejection time (up to an 80 ms) and stroke volume (up to 9.7 mL), with a small fall in heart rate (up to 2.7 beats per min; $p < 0.0001$ for all three measures).^[40] A dose-finding study in patients with acute heart failure (ATOMIC-AHF) is currently enrolling, and the high bioavailability of oral omecamtiv mecarbil presents the potential for chronic oral administration of this therapy.

Other potential new inotropic mechanisms include sodium–potassium–adenosine triphosphatase (ATPase) inhibition with SERCA activation (istaroxime), SERCA activation with vasodilation (nitroxyl donors such as CXL-1020), ryanodine receptor stabilization (S44121), and energetic modulation (etomoxir; pyruvate).^[41]

Load reduction and vasodilation

Principles of load reduction

Once a specialized procedure, vasodilation is now commonplace in the therapy of heart failure and hypertension, as the peripheral circulation has become one of the prime sites of cardiovascular drug action. Vasodilators may be classified according to the site of action in the circulation (see Fig. 2-3). Preload reducers (predominantly venodilators) may be separated from those primarily reducing the afterload (predominantly arteriolar dilators), whereas mixed agents act on both pre- and afterload and are combined veno-arteriolar dilators. ACE inhibitors can be regarded as specialized vasodilators that have many other additional properties (see Chapter 5). Whereas other vasodilators, especially the arteriolar dilators, reflexly activate the renin-angiotensin axis, ACE inhibitors both vasodilate and inhibit this system, besides having sympatholytic properties.

Preload reduction.

Normally as the preload (the LV filling pressure) increases, so does the peak LV systolic pressure, and the cardiac output rises (ascending limb of the Frank-Starling curve). In diseased hearts the increase in cardiac output is much less than normal, and the output fails to rise and may even fall as the filling pressure rises (the apparent descending limb of Frank-Starling curve). However, the optimal filling pressure for the diseased heart is extremely variable, not always being higher than normal. Reduction of the preload is generally but not always useful. Clinically, the major drugs that reduce the preload in heart failure are (1) furosemide by its diuretic effect, and (2) the nitrates that dilate the systemic veins to reduce the venous return and thus the filling pressure in both the right and left heart chambers.

Afterload reduction.

The therapeutic aim of afterload reduction is to decrease the peripheral vascular resistance to lessen the load on the heart, improve renal function, and improve skeletal muscle perfusion. Reduction of the systemic (peripheral) vascular resistance is not the same as BP reduction because in heart failure a compensatory increase in the cardiac output tends to maintain the arterial pressure during afterload reduction. Specific afterload reducers are few and limited in practice to two. First, hydralazine is a nonspecific agent with a cellular mode of action that is still undetermined, although it may well act as a potassium channel opener. Second, the calcium channel blockers (CCBs) are afterload reducers and widely used in hypertension. They often have a negative inotropic effect, thereby restricting their use in heart failure, in which they are as a group contraindicated. Amlodipine and other long-acting CCBs may be an exception, although with severe restrictions (see Chapter 3).

Combined preload and afterload reduction.

Sodium nitroprusside, used for very severe hypertension or CHF, must be given intravenously under close supervision and careful monitoring. The α -adrenergic blockers give combined pre- and afterload reduction, the latter explaining their antihypertensive effect. Theoretically, they should also work in CHF but do not. Rather, as a group they increase the incidence of heart failure when given as monotherapy for hypertension (see Chapter 7, p. 251). Of the two combined α - and β -blockers, labetalol and carvedilol, only the latter is well tested in heart failure (see Fig. 1-10). The β -blocking component of these drugs should be able to inhibit β -mediated myocardial toxicity resulting from neuroadrenergic activation in heart failure, and the α -blocking component to reduce peripheral vasoconstriction.

Nitroprusside: The prototype balanced vasodilator

Nitroprusside is a donor of NO that vasodilates by formation of cyclic guanosine monophosphate (GMP) in vascular tissue (Fig. 6-6). Intravenous sodium nitroprusside remains the reference vasodilator for severe low output left-sided heart failure, provided that the arterial pressure is reasonable, because it acts rapidly and has a balanced effect on the afterload and preload (see Fig. 2-3), dilating both arterioles and veins. Nitroprusside, an ultra-rapid agent, seems particularly useful for increasing LV stroke work in acute severe refractory heart failure caused by mitral or aortic regurgitation. Hemodynamic and clinical improvements are also observed in patients with severe pump failure complicating AMI, in heart failure after cardiac surgery, and in patients with acute exacerbation of chronic heart failure. Because of the need for careful, continuous monitoring and its light sensitivity, as well as the risk of cyanide toxicity,^[42] nitroprusside is being replaced in severe acute-on-chronic heart failure by nitrates, and in hypertensive crises by intravenous nicardipine, fenoldopam, or labetalol (see Table 7-4). However, at many specialized heart failure centers, nitroprusside remains a frequently used agent, supported by the results of a nonrandomized study in 175 patients with acute decompensated heart failure and a cardiac index of 2 L/min/m² or less admitted for intensive medical therapy including vasoactive drugs. The nitroprusside-treated patients had greater hemodynamic improvement and lower rates of all-cause mortality than the control patients.^[43]

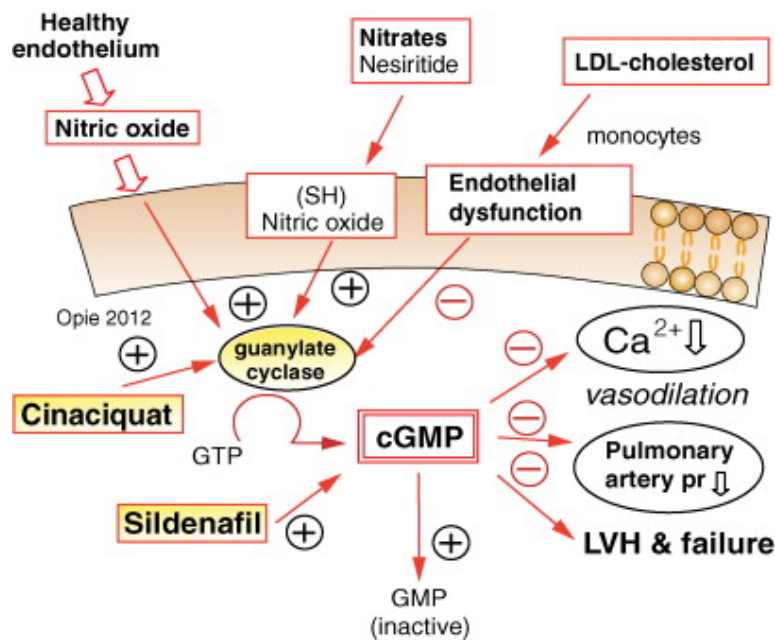


Figure 6-6 Nitric oxide, nitroprusside, and nesiritide stimulate guanylate cyclase to form cyclic guanosine monophosphate with vasodilatory properties. Note possible role of sildenafil and related compounds (see Fig. 2-6). cGMP, Cyclic guanosine monophosphate; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; SH, Sulfhydryl. (Figure © L.H. Opie, 2012.)

Properties, precautions, and cyanide toxicity.

With infusion of nitroprusside, the hemodynamic response (direct vasodilation) starts within minutes and stops equally quickly. Nitroprusside given intravenously is converted to cyanmethemoglobin and free cyanide in the red cells; the free cyanide is then converted to thiocyanate in the liver and is cleared by the kidneys (half-life of 7 days). Extravasation must be avoided. The solution in normal saline (avoid alkaline solutions) must be freshly made and then shielded from light during infusion; it should be discarded when 4 hours old, or before if discolored. *Toxicity* is a special problem with nitroprusside particularly when given at high doses or for long periods and especially if there is liver or renal failure to limit cyanide metabolism and excretion of end products.

Cyanide toxicity: Cyanide accumulation can kill cells by inhibition of oxidative metabolism, which leads to anaerobic metabolism with lactic acidosis. This sequence is potentially fatal. However, the latter may be a terminal event more related to circulatory failure. The clinical picture is variable and ranges from abdominal pain to unexplained death. Nervous system features are prominent and include changed mental status, unexplained encephalopathy, focal lesions, convulsions (cyanide apoplexy), and even brain death.^[42] Cyanide toxicity can be avoided by (1) keeping the infusion dose as low and as short as possible, and no longer than 10 minutes at top dose in the treatment of severe hypertension; (2) maintaining clinical suspicion; (3) giving concomitant sodium thiosulfate; and (4) searching for indirect evidence of toxicity such as increasing blood lactate and blood thiocyanate levels. Using the latter, it is sometimes permissible to use low-dose nitroprusside for up to 3 days when using this agent as a bridge to a mechanical assist device or to transplantation (see "Nitroprusside: Doses, Indications, and Contraindications" later in this chapter). However, thiocyanate levels only indirectly reflect cyanide toxicity and give imperfect guidance. **Thiocyanate toxicity** is another hazard (toxic thiocyanate level 100 mcg/mL). Thiocyanate is relatively nontoxic, but can become so in the presence of renal failure, giving a variety of gastrointestinal (GI) and central nervous features, some of which overlap with cyanide toxicity.

Nitroprusside: Doses, indications, and contraindications.

The usual dose is 0.5-10 mcg/kg/min, but infusion at the maximal rate should never last for more than 10 minutes. The package insert gives a boxed warning that, except when used briefly or at very low rates (<2 mcg/kg/min), toxic cyanide can reach potentially lethal levels. The infusion rate needs careful titration against the BP, which must be continuously monitored to avoid excess hypotension, which can be fatal. When treating severe hypertension, the package insert warns that if the BP has not been adequately controlled after 10 minutes of infusion at the maximal rate, the drug should be stopped immediately. Conversely, nitroprusside must not be abruptly withdrawn during the treatment of heart failure because of the danger of rebound hypertension.

Indications include the following situations: (1) severe acute-on-chronic heart failure, especially with regurgitant valve disease, to “rescue” the patient or to act as a bridge to transplantation or to a mechanical assist device; (2) in hypertensive crises (see Table 7-4); (3) in dissecting aneurysm; (4) for controlled hypotension in anesthesia (maximum dose 1.5 mcg/kg/min); and (5) after coronary bypass surgery, when patients frequently have reactive hypertension as they are removed from hypothermia, so that nitroprusside or nitrates may be given for 24 hours provided that hypotension is no problem. *Contraindications* are as follows: preexisting hypotension (systolic < 90 mm Hg, diastolic < 60 mm Hg). All vasodilators are contraindicated in severe obstructive valvular heart disease (aortic or mitral or pulmonic stenosis, or obstructive cardiomyopathy). Unexpectedly, carefully monitored nitroprusside can improve cardiac output in very tight aortic stenosis with severe heart failure, acting as a bridge to valve replacement and showing that an increased total vascular resistance contributes to the load on the suffering left ventricle.^[44] AMI is not a contraindication, provided that excess hypotension is avoided. Nitroprusside is contraindicated in hepatic or renal failure because clearance of toxic metabolites is depressed.

Side effects of nitroprusside.

Side effects of nitroprusside besides cyanide toxicity, are as follows. Overvigorous treatment may cause an excessive drop in LV end-diastolic pressure, severe hypotension, and myocardial ischemia. Fatigue, nausea, vomiting, and disorientation caused by toxicity tend to arise especially when treatment continues for more than 48 hours. In patients with renal failure, thiocyanate accumulates with high-dose infusions and may produce hypothyroidism after prolonged therapy. Hypoxia may result from increased ventilation-perfusion mismatch with pulmonary vasodilation.

Treatment of cyanide toxicity.

First, be vigilant to avoid cyanide toxicity. Discontinue the infusion once the diagnosis is suspected (blood thiocyanate levels are only an indirect guide). Give sodium nitrite 3% solution at less than 2.5 mL/min to total dose of 10 to 15 mL/min, followed by an injection of sodium thiosulfate, 12.5 g in 50 mL of 5% dextrose water over 10 min. Repeat if needed at half these doses.

Nitrates

Nitrates are now used in the therapy of both acute and chronic heart failure (see Chapter 2, p. 50). They work increasing vasodilatory vascular cyclic GMP. Their major effect is venous rather than arteriolar dilation, thus being most suited to patients with raised pulmonary wedge pressure and clinical features of pulmonary congestion. Nitrates produce a “pharmacologic phlebotomy.” Intravenous nitrates are usually chosen instead of nitroprusside for acute pulmonary edema of MI because of the extensive experience with nitrates in large trials. Besides acting as vasodilators, nitrates may oppose the harmful growth-promoting effects of norepinephrine, raised in heart failure, on cardiac myocytes and fibroblasts.^[45] As noted previously, intravenous nitrates were demonstrated to be superior to diuretics alone in patients with heart failure and acute pulmonary edema.^[15] In the VMAC trial, very low doses of intravenous nitroglycerin showed no significant difference from placebo in early dyspnea relief or reduction in pulmonary capillary wedge pressure (PCWP).^[46] However, a small subgroup analysis from VMAC in which nitroglycerin was more aggressively up-titrated^[47] demonstrated that higher-dose intravenous nitroglycerin significantly improved PCWP, although tachyphylaxis was evident at 24 hours.^[47] Intravenous nitroglycerin is probably underused in the United States. When administered for acute heart failure, starting doses should be from 20-40 mcg/min with rapid up-titration every 5-10 minutes to the desired hemodynamic or symptom effect up to approximately 200 mcg/min. The main side effects are headache and hypotension, both of which respond to decrease or cessation of the infusion.

Nesiritide

Nesiritide is the first of a new drug class of therapeutic NPs to be approved in the United States. It is a recombinant preparation of the human B-type natriuretic peptide identical to the endogenous hormone produced by the ventricles in response to increased wall stress and volume overload. In an early study, nesiritide, when added to standard therapy of acute heart failure by intravenous or oral diuretics, gave greater relief of dyspnea than did nitroglycerin.^[46] Nesiritide increased peak expiratory flow rate with acute heart failure treatment during the first 24 hours.^[48]

A metaanalysis of five studies in 2005 raised the risk of worsening renal function,^[49] as well as increased mortality.^[50] The definitive, randomized trial (ASCEND-HF) compared nesiritide to placebo in addition to standard therapy in 7141 patients and showed that patients treated with nesiritide had minimal improvement in dyspnea and no beneficial effect on hospitalizations for heart failure or death within 30 days. Although there was an increased incidence of symptomatic hypotension in the nesiritide group, there were no differences in the rates of worsening renal function.^[51]

Investigational vasodilators

Given the central role of vasodilator therapy in acute heart failure, there has been considerable enthusiasm for developing other types of vasodilator therapies, including other chimeric NPs (e.g., cenderitide) and soluble guanylate cyclase activators or stimulators (e.g., cinaciguat). Another novel investigational agent is relaxin, a pleiotropic neurohormone with vasodilating and potentially renoprotective effects, which had encouraging results in early studies^[52] and is currently in Phase III trials.^[53]

Vasopressin and “vaptans”

Vasopressin receptors.

Vasopressin, or antidiuretic hormone (ADH), is synthesized in the hypothalamus and is crucial for osmoregulation, cardiovascular tone, and homeostasis (Fig. 6-7). Previous clinical studies have highlighted the role of vasopressin and its analogues in cardiopulmonary resuscitation (CPR), septic shock, and intraoperative hypotension.^{[54],[55]} Recently, emphasis has shifted to syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH), as reviewed by Gassanov and colleagues.^[56]

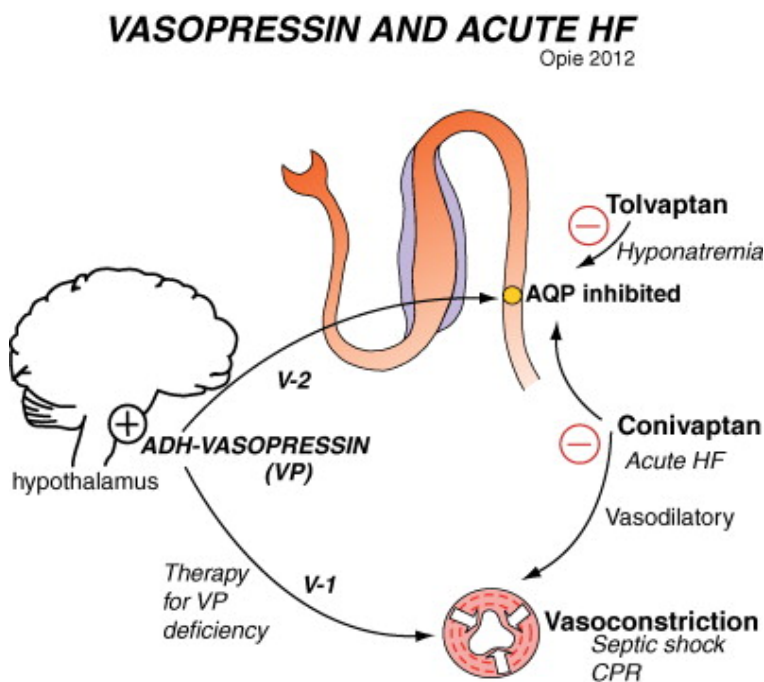


Figure 6-7 Vasopressin and heart failure. Note use of V-1 agonists for selected types of acute heart failure, and of V-2 antagonists for aquaporin (AQP) inhibition and vasodilation. ADH, antidiuretic hormone; AQP, Aquaporin; CPR, cardiopulmonary resuscitation. (Figure © L.H. Opie, 2012.)

ADH is released in response to increased plasma osmolality, decreased arterial pressure, and reduced cardiac filling. Human ADH contains arginine, and is called *arginine vasopressin (AVP)* to distinguish it from other vasopressin analogues. Three subtypes of vasopressin receptors have been identified: V₁, V₂, and V₃. V₁ receptors are G-coupled proteins that operate via the phosphoinositide signaling pathway, causing release of intracellular calcium and vasoconstriction. V₂ receptors are also coupled to G proteins, but operate via adenylyl cyclase, using cAMP as a secondary messenger. V₂ receptors are found in renal tubules, and mediate water retention. V₃ receptors in the anterior pituitary gland are associated with corticotropin (adrenocorticotropic hormone) release and are not discussed here.

At present, no enzymes have been specifically linked to vasopressin formation or degradation. Thus most research into pharmacologic manipulation of vasopressin has focused on identifying vasopressin receptor agonists and antagonists (see Fig. 6-4).

Effects of arginine vasopressin on vascular tone.

Intravenous administration of AVP has rapid onset (minutes) and is quickly distributed from the plasma to

extracellular volume. Most clearance occurs as a result of liver and kidney metabolism, and a small portion of clearance is due to renal elimination. The half-life is brief (4-20 minutes), and AVP must therefore be given as a continuous intravenous infusion to maintain physiologic effects. The effects of the vasopressin system are mitigated when the sympathetic nervous system, the renin-angiotensin system (RAS), and the neurohormonal systems are intact. AVP release appears to be more tightly related to maintenance of circulating blood volume than to preserving arterial pressure. Severe increases in plasma AVP levels usually occur with profound hypotension, hemorrhagic shock, and cardiac arrest. Yet comparatively low AVP levels have been reported in patients with septic shock and in hemodynamically unstable organ donors, suggesting that clinical states of "relative vasopressin deficiency" may exist, and that these might respond to exogenous vasopressin administration. AVP has thus been relatively recently introduced in clinical practice as a vasopressor for several specific settings: intraoperative hypotension, vasodilatory shock, septic shock, and during CPR (see later). Adverse outcomes have included GI ischemia, renal ischemia, biventricular dysfunction,^[57] reduced cardiac index, reduced total oxygen delivery, and reduced oxygen uptake.

Arginine vasopressin for cardiopulmonary resuscitation and shock.

In both human and animal models, administration of exogenous AVP during CPR results in increased coronary perfusion pressure and improved resuscitation outcomes. Vasopressin is superior to epinephrine in increasing vital organ blood flow and improving resuscitation outcomes. The previous American Heart Association (AHA) Guidelines for CPR recommended either repeated 1-mg boluses of epinephrine or replacing the first or second dose of epinephrine with one bolus of 40 U of vasopressin or using vasopressin preferentially for asystole (see seventh edition Figs. 12-10 and 12-11). AVP has been used to treat hypotension after cardiopulmonary bypass, which appears to be associated with low circulating vasopressin levels. In doses of 0.1 U/min, vasopressin improves postcardiotomy shock in both adults and children.

Vaptans for hyponatremia.

Two vasopressin antagonists ("vaptans") are now in the market for the treatment of euvoletic (Europe) or euvolemic and hypervolemic (United States) hyponatremia: conivaptan for intravenous use and tolvaptan for oral application. Both drugs are approved for (1) the treatment of hyponatremia caused by SIADH, and (2) hyponatremia caused by CHF and hepatic cirrhosis.^[58] Gross and Wagner pose three questions.^[59] (1) Do these drugs decrease the high mortality associated with hyponatremia? (2) Is it justifiable to use them to prevent relapse of hyponatremia in chronic SIADH? (3) Can the cost of chronic vaptan therapy be justified? They comment that the optimal vaptan regimen (dose, timing of controls) to treat SIADH is currently not established, nor is the best procedure to avoid over-rapid correction of chronic hyponatremia. Thus these authors "are hesitant to consider vaptans a treatment of choice (even) for the appropriate hyponatremias."

Conivaptan for hyponatremia in heart failure.

Conivaptan (Vaprisol) is a renal V₂ receptor antagonist approved in the United States for treatment of *euvolemic hyponatremia* (serum sodium <135 mEq/L) in hospitalized patients with underlying heart failure. The expected clinical benefit of raising serum sodium might outweigh the increased risk of adverse events, including infusion site phlebitis, hypokalemia, headache, and neurologic deficits (from over-rapid correction of hyponatremia), although this hypothesis has not been adequately demonstrated in clinical trials. *Dosing of conivaptan*: an intravenous 20-mg loading dose over 30 minutes is followed if needed by a 20 mg continuous intravenous infusion over 24 hours. This may be titrated to 40 mg/day if serum sodium does not rise at the desired rate.

Tolvaptan for hyponatremia in heart failure.

Tolvaptan (15-60 mg daily) is an oral V₂ antagonist that increased serum sodium on days 4 and 30 of administration in the SALT study.^[60] In heart failure patients with signs of volume overload and on a low-sodium diet, tolvaptan monotherapy, without concomitant loop diuretic therapy, reduced body weight when compared with placebo without adverse changes in serum electrolytes, while on background medications including ACE inhibitors and β -blockers.^[61] However, in the EVEREST study, despite short-term beneficial weight loss and mild improvement in dyspnea,^[62] there was no long-term benefit on mortality or morbidity in heart failure.^[63] The Food and Drug Administration (FDA)-approved indication is for hyponatremia (<125 mEq/L) that is symptomatic and resistant to fluid restriction. The black box warns against too-rapid correction that can cause osmotic demyelination.

Other vaptans.

Other vaptans include mozavaptan, lixivaptan, and satavaptan, all acting on the V₂ receptor.

Future directions

In addition to the new approaches noted previously, a number of intriguing therapeutic directions are currently under development. Therapies directed toward cardioprotection and *improved metabolic status* of the myocardium (e.g., pyruvate, etomoxir) are emerging as potential drugs for acute heart failure. Glucose-insulin-potassium (GIK) treatment was compared with placebo in 217 patients undergoing aortic valve replacement for critical aortic stenosis and evidence of LV hypertrophy.^[64] GIK treatment reduced the incidence of low cardiac output (odds ratio, 0.22; $P = 0.0001$) and reduced inotrope use 6 to 12 hours postoperatively (odds ratio, 0.30; 95% confidence interval [CI], 0.15 to 0.60; $P = 0.0007$) and LV biopsies showed increased molecular markers of cardioprotection (adenosine monophosphate kinase, Akt phosphorylation, and O-linked N-acetylglucosamine [O-GlcNAc]-ylation of selected protein bands). Long-term studies are underway with this and other therapies to provide cardioprotection during acute heart failure. *Neurohumoral activation* includes activation of the inflammatory and immune system, as suggested by elevated levels of C-reactive protein, interleukin-6, and tissue plasminogen activator levels, all of which correlated with 180-day mortality.^[65]

Novel approaches to increasing cardiac performance

As noted previously, all of the currently available inotropes and inodilators operate via a mechanism that increases intracellular cAMP and calcium with resultant increases in heart rate, myocardial oxygen demand with consequent increases in ischemia, arrhythmias, and death. Multiple new approaches have been developed to improve cardiac performance potentially without these liabilities. *Aliskiren*, the direct renin inhibitor, is under test in the ASTRONAUT study, the hypothesis being that it will oppose the abnormal neurohumoral abnormalities present in acute heart failure.

Direct activation of cardiac myosin is one promising approach. Two human studies report the effects of the cardiac myosin activator, *omecamtiv mecarbil*, in volunteers or in patients with systolic heart failure. The first-in-man (34 healthy men) study showed highly dose-dependent increased LV systolic function in response to intravenous omeamtiv mecarbil and supported potential clinical use of the drug in patients with heart failure.^[39]

In an associated article on 45 patients with stable, guideline-treated systolic heart failure, intravenous omeamtiv mecarbil gave concentration-dependent increases in LV ejection time (up to an 80 ms) and stroke volume (up to 9.7 mL), with a small fall in heart rate (up to 2.7 beats per min; $p < 0.0001$ for all three measures). A dose-finding study in patients with acute heart failure (ATOMIC-AHF) is currently enrolling, and the high bioavailability of oral omeamtiv mecarbil indicates a potential use in chronic oral administration.^[40]

Other potential new inotropic mechanisms include sodium-potassium-ATPase inhibition with SERCA activation (istaroxime), SERCA activation with vasodilation (nitroxyl donors such as CXL-1020), ryanodine receptor stabilization (S44121), and energetic modulation (etomoxir, pyruvate).^[41]

Cardiogenic shock

In cardiogenic shock the major goals are load reduction, preservation of cardiac function, and maintenance of an optimal BP so as to promote renal perfusion. Preload reduction by urgent reduction of pulmonary capillary pressure and right atrial filling pressure is sought along with a positive inotropic effect. Depending on the BP, the afterload might either have to be reduced by vasodilation, or sometimes increased by peripheral vasoconstriction. These aims can be achieved by a variety of intravenous inotropes, including dopamine, dobutamine, milrinone, and others. Some of these, such as high-dose dopamine and norepinephrine, cause α -mediated vasoconstriction to increase the BP in shocklike states. The inotropic dilators, such as milrinone, and low-dose dopamine, have a prominent vasodilator component to their inotropic action that is desired if the BP is relatively well maintained. Cardiogenic shock carries a poor prognosis despite the use of any or many drug treatments. Assist systems such as intraaortic balloon pumping (IABP-SHOCKII trial) are increasingly used and are under trial.

Chronic heart failure

Chronic heart failure differs from acute failure in the emphasis of therapy. In acute heart failure, the aim is to provide immediate symptomatic relief, and to rescue the patient from imminent and short-term cardiorespiratory death by optimizing the hemodynamic and neurohormonal status, and to prevent acute myocardial, renal, and other end organ damage. The emphasis is on agents given intravenously. In chronic heart failure, the objectives are to prevent chronic progressive damage to the myocardium (prevention), to prevent or reverse further enlargement of the heart (reverse remodeling), to improve the quality of life by relief of symptoms, and to prolong life. Reduction of hospitalization is an important goal for health providers because that is the major determinant of cost relating to the management of heart failure. The origin of symptoms in chronic heart failure is still not well understood.

Successive pivotal trials have now established, first, the disabling nature of conventionally treated CHF if left to run its natural course, and, second, that certain agents can partially reduce the increased mortality. The most effective drugs act largely by modulating the neurohumoral responses in heart failure (see Fig. 5-8). The key drugs are diuretics, ACE inhibitors, β -blockers, aldosterone inhibitors (spironolactone and eplerenone), and angiotensin receptor blockers (ARBs), as well as the combination of hydralazine and nitrates in select patients. Diuretics provide symptomatic relief from fluid overload. A second group of drugs comprises agents that have positive inotropic effects and generally increase cell cAMP and calcium levels, which tend to increase mortality. Most of these agents increase mortality in chronic heart failure probably as a result of worsening myocardial damage, promotion of apoptosis, and arrhythmogenesis. Digoxin has characteristics of both groups, because it both inhibits the neurohumoral response and has a positive inotropic effect. These properties might explain why it had an overall neutral effect on mortality in some studies.

Therapy of chronic severe heart failure

When the acute phase is over, the patient is often left with chronic severe heart failure that requires a different management policy. That policy is almost the same as in patients presenting initially with chronic heart failure. The diagnosis must be established with certainty, the causal factors determined, concomitant disease identified and treated, and an assessment of symptom severity and prognosis made. Symptomatic therapy is aimed at achieving optimal diuresis to treat or prevent sodium and water retention. The intention is to restore body fluid volumes and distribution to normal and not to over-diurese the patient. The disadvantageous neurohumoral response is inhibited by ACE inhibition, ARBs, β -blockade and aldosterone inhibitors (spironolactone or eplerenone) (see Fig. 5-8). Digoxin may be used for the control of heart rate in atrial fibrillation and might contribute in sinus rhythm by acting as a sympathoinhibitory agent (but see major reservations in "Digoxin in Perspective" later in this chapter). Drugs should be used in the lower doses effective in the major trials.

Current trends.

Although the myocardium might be largely destroyed, symptomatic improvement is still possible using a judicious mixture of diuretics, ACE inhibition, β -adrenergic blockade, spironolactone-eplerenone, ARBs, and vasodilators such as isosorbide-hydralazine for selected patients (see Figs. 2-7 and 6-10). Overall, the strategy is to rest the feeble myocardium and to avoid stimulation. Drugs such as the ACE inhibitors, β -blockers, spironolactone-eplerenone, and isosorbide-hydralazine improve prognosis, whereas diuretics relieve fluid retention and dyspnea, and yet others may be harmful (Table 6-4). The most significant recent change to therapy of chronic heart failure is the increasing addition of aldosterone blockers after ACE inhibitors and β -blockers. Ivabradine may be emerging as another important additional therapy on top of the maximally tolerated three-drug regimen. Multiple other approaches are being investigated, including metabolic therapies (e.g., perhexiline and trimetazidine) and sildenafil (see Fig. 6-6). The many exciting recent advances in the domains of device and gene therapy are beyond the scope of this chapter.

Table 6-4 -- Chronic Heart Failure: Drugs That Reduce Mortality, Improve Symptoms, or Might Harm

Reduce Mortality; Must Try to Use
<ol style="list-style-type: none"> 1. ACE inhibitors or ARBs 2. β-blockers 3. Spironolactone or eplerenone 4. Isosorbide-hydralazine (well tested in black patients)
Improve Symptoms; Use According to Clinical Judgment
<ol style="list-style-type: none"> 1. Diuretics 2. Nitrates 3. Iron for anemia 4. Metabolically active agents (if available: trimetazidine, perhexiline) 5. Ivabradine
May be Harmful; Use Cautiously after Due Consideration
<ol style="list-style-type: none"> 1. Inotropes and inotropic dilators 2. Antiarrhythmics, except β-blockers and amiodarone 3. Calcium channel blockers 4. Digoxin, after checking levels of potassium and creatinine, only in low doses aiming at blood levels of 0.65-1.3 nmol/L (0.5-1 ng/mL). High-dose digoxin, with blood levels of 1.3 to 2.6 nmol/L (1-2 ng/mL), previously acceptable, no longer is.

Table created by P.J. Commerford, modified by L.H. Opie.

ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Incremental therapy.

Incremental therapy can counter the full downward evolution of progressive heart failure by matching drugs to the stage of heart failure (Table 6-5). Stage A is largely preventative. Stage B adds more active neurohumoral inhibition. Stage C includes diuretic therapy, aldosterone inhibitors, biventricular pacing (cardiac resynchronization therapy [CRT]) and implantable cardioverter defibrillators (ICDs) (see Fig. 8-16). Intervention increases in stage D to include left ventricular assist devices (LVADs) and heart transplantation, with the increasing exploration of stem-cell therapy.

Table 6-5 -- ACC-AHA Recommended Treatment of Chronic HF

STAGE A:
<ul style="list-style-type: none"> • Treat hypertension • Quit smoking • Treat lipids • Exercise • Discourage alcohol intake and illicit drug use • ACE inhibitors or ARBs
↓ Structural Heart Disease Develops
STAGE B:
<ul style="list-style-type: none"> • Stage A therapy • ACE inhibitors or ARBs • β-blockers
↓ Heart Failure Symptoms Develop
STAGE C:

<ul style="list-style-type: none"> • Stage A therapy • Diuretics • ACE inhibitors or ARBs • β-blockers • Digoxin • Aldosterone antagonist • Hydralazine, nitrates • Salt restriction • Biventricular pacing, ICD
↓ Refractory Symptoms at Rest
STAGE D:
<ul style="list-style-type: none"> • Stage C therapy • Mechanical assist devices • Heart transplantation • Continuous inotropic infusions • Hospice care

ACC, American College of Cardiology; ACE, angiotensin-converting enzyme; AHA, American Heart Association; ARB, angiotensin receptor blocker; HF, heart failure; ICD, implantable cardiac defibrillator.

Heart failure: Therapy specifics

General measures and lifestyle modification.

General measures and lifestyle modification include mild salt restriction, water restriction in the presence of poor renal perfusion, and aspirin.^[66] Warfarin gave equal overall benefit, with better reduction of stroke at the cost of more GI hemorrhage. Although periodic bed rest may be required to achieve optimal diuresis (the patient returning to bed for 1 to 2 hours of supine rest after taking the diuretic), in principle physical activity should be maintained; there is strong evidence that an exercise rehabilitation program should be undertaken if possible.^[67] Exercise training for 12 months in those with well-treated chronic heart failure of median age 59 years was associated with modest 11%-15% reductions for both all-cause mortality or hospitalization, and cardiovascular mortality or heart failure hospitalization at 30 months.^[68] There were similar modest reductions in patient-reported health status.^[69] One of the most cost-effective of the new approaches to CHF is *home-based intervention* by a cardiac nurse, which reduced hospitalization and improved event-free survival.^[70] Such home nursing visits give advice and support and oversee drug therapy, which is often very complex in advanced heart failure. A further example of the value of excellent nursing is the multidisciplinary nurse-coordinated heart failure management program that reduced mortality risk and surrogate markers of well being.^[71]

Advice should be given on flu immunization, alcohol consumption, cessation of smoking, sexual activity, diet, drug interactions, exercise, flying, lifestyle, and risk factors. *Anemia* is now recognized as an adverse risk prognostic factor^[72] and may warrant therapy, as ongoing trials will assess the benefit of erythropoietin-stimulating agents and iron (see later).

Diuretic doses.

Diuretic doses must be carefully adjusted to steer the course between optimal relief of edema and excess diuresis, polydiuresis, ionic disturbances, and prerenal azotemia. In older adults, excess use of diuretics can lead to tiredness and fatigue. Following the principle of sequential nephron blockade (see Fig. 4-2) combination diuretic therapy is often required and is usually more comfortable for patients. In those unusual patients who have severe heart failure with major reduction of the glomerular filtration rate (GFR; less than 15 to 20 mL/min), high doses of furosemide alone or more often combined with a thiazide diuretic are used. In severe fluid overload, intravenous loop diuretics may be used more often.^{[8],[73]} Metolazone is a powerful

diuretic used in difficult resistant cases. Potassium-sparing diuretics, such as spironolactone and eplerenone, are often combined with those diuretics that do not spare potassium. In diuretic-resistant patients, first check for interacting drugs, especially nonsteroidal antiinflammatory drugs (see Fig. 4-5). Oral furosemide has variable absorption characteristics and occasionally the patient may benefit by a change to the better-absorbed torsemide.^[74]

β-blockers.

Historically coming after the ACE inhibitors, β-blockers have reduced mortality substantially. Standard heart failure therapy is diuretics, renin-angiotensin-aldosterone system (RAAS) inhibition, and β-blockers. In early heart failure β-blockade may be considered as early therapy, even before an ACE inhibitor,^{[75],[76]} the logic being that the earliest neurohumoral adaptation in is baroreflex-induced adrenergic stimulation (see Fig 5-8). The specific agents tested in chronic heart failure are bisoprolol (CIBIS I and II), metoprolol succinate (MERIT-HF), and carvedilol (US Carvedilol Study, Australia-New Zealand Study, COPERNICUS, and CAPRICORN), with doses as given in Table 1-2. Nebivolol given to older adults in heart failure reduced hospitalization but not mortality.^[77] All patients with chronic heart failure and significantly reduced LV systolic function should be considered for a β-blocker. The patient should be hemodynamically stable when treatment is initiated. β-blockade is not a “rescue” treatment for more severe heart failure. Even class IV patients can substantially benefit from a β-blocker with improved morbidity and mortality, specifically carvedilol (COPERNICUS).^[78] It is essential to start with a very low dose of the β-blocker, and then to titrate the dose upward slowly and steadily over many weeks. Incremental increases of dose should not be undertaken in less than 2 weeks. Doses should be titrated to the maximally tolerated dose up to the target doses from the relevant clinical trials (see Table 1-3). Many patients may have mild increases in fatigue with initiation of β-blockers, but this effect is usually transient and with proper counseling and preparation, they are generally well tolerated.^[79]

Update: New Content Added

Date Added: 07 February 2013

Beta-2 Adrenergic signaling links upregulation of G protein-coupled receptor kinase 2 to heart failure

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Summary

Background. Can lifestyle intervention achieve remission in type 2 diabetes?

Background:. Upregulation of G protein-coupled receptor kinase 2 (GRK2) is a well-established causal factor of heart failure, but the underlying mechanism is poorly understood. See Figs. 1-6 and 1-7 in this book.

Methods and Results: The authors state as follows:“ Overexpression of GRK2 led to a G(i)-dependent decrease of contractile response to βAR stimulation in cultured mouse cardiomyocytes and in vivo. Importantly, cardiac-specific transgenic overexpression of a mutant β(2)AR lacking PKA phosphorylation sites (PKA-TG) but not the wild-type β(2)AR (WT-TG) or a mutant β(2)AR lacking GRK sites (GRK-TG) led to exaggerated cardiac response to pressure overload, as manifested by markedly exacerbated cardiac maladaptive remodeling and failure and early mortality. Furthermore, inhibition of G(i) signaling with pertussis toxin restores cardiac function in heart failure associated with increased β(2)AR to G(i) coupling induced by removing PKA phosphorylation of the receptor and in GRK2 transgenic mice, indicating that enhanced phosphorylation of β(2)AR by GRK and resultant increase in G(i)-biased β(2)AR signaling play an important role in the development of heart failure.”

Comment:

This is an important paper to clarify the contradictory effects of beta-stimulation, both physiologically increasing the inotropic state while playing a role in the development of heart failure For the clinician, this study gives mechanistic support for the use of combined alpha-beta blockers such as carvedilol in

the therapy of heart failure...

The authors summarize as follows: "Our data show that enhanced $\beta(2)$ AR phosphorylation by GRK, in addition to PKA, leads the receptor to G(i)-biased signaling, which, in turn, contributes to the pathogenesis of heart failure, marking G(i)-biased $\beta(2)$ AR signaling as a primary event linking upregulation of GRK to cardiac maladaptive remodeling, failure and cardiodepression."

References

1. Zhu W, Petrashevskaya N, Ren S, et al: Gi-biased β 2AR signaling links GRK2 upregulation to heart failure. *Circ Res* 2012; 110:265-274.

Which β -blocker?

The appropriate β -blocker remains under debate, but we are impressed with the overall positive data for carvedilol,^[80] including its antioxidant properties.^[81] At present the standard therapy is that a β -blocker is added to earlier treatment with an ACE inhibitor. However, given that increasing ACE inhibitor doses improved hospitalizations but had less effect on mortality,^[82] whereas β -blocker in addition to ACE inhibitors had dramatic effects on reducing mortality, many clinicians initiate a low dose of ACE inhibitor followed by full up-titration of a β -blocker prior to up-titrating the ACE inhibitor. In addition, some emerging evidence suggests that the order of initial ACE inhibitor or β -blocker therapy may not matter.^[75]

Added heart rate reduction: Ivabradine.

Higher heart rates are a risk factor for adverse outcomes in heart failure.^[83] Ivabradine is a first-in-class specific inhibitor of the sinus node *I_f* current, which selectively decreases heart rate with no known off-target myocardial, vascular, or other adverse effects. This unique agent allowed the investigators of SHIFT to test the effect of solely reducing heart rate on outcomes. In the 6558-patient SHIFT study, ivabradine, added to standard therapy of chronic heart failure patients with a persistent heart rate of 70 bpm or higher, reduced the combined endpoint of cardiovascular death or hospital admission for heart failure (hazard ratio [HR] 0.82; CI: 0.75-0.90; $p < 0.0001$) compared with placebo, but had no significant effect on cardiovascular or all-cause mortality.^[84] Ivabradine was titrated to a maximum of 7.5 mg twice daily. Side effects were excess bradycardia in 5% versus 1% of patients with placebo; visual side effects (phosphenes) occurred in 3% of patients versus 1% with placebo.

In the *Lancet* editorial, Teerlink expressed the concern that despite the admonitions of the SHIFT investigators, clinicians might be tempted to substitute ivabradine for β -blockers or fail to aggressively uptitrate β -blocker therapy prior to initiating ivabradine.^[85] β -blockers have demonstrated marked improvement in survival in many trials with mortality risk reductions of 24%-65%, whereas ivabradine did not demonstrate improved survival in either the 10,917 patient BEAUTIFUL trial or in the 6558-patient SHIFT trial. These trial data suggest that β -blockers confer a survival benefit that may not be provided by ivabradine. Only 23% of the patients in SHIFT were at target dose and only half were receiving 50% or more of the targeted β -blocker dose. In a recent publication from SHIFT, it was noted that the beneficial effect of ivabradine progressively decreased in patients on increasing baseline doses of β -blocker, such that in the 1488 patients at target dose β -blocker, there was no benefit of ivabradine on the combined endpoint of cardiovascular mortality or heart failure hospitalization (HR 0.99, CI 0.79-1.24, $p = 0.91$) and certainly no indication of a beneficial effect on all-cause mortality (HR 1.08, 0.78-1.48, $p = 0.65$).^[86] Therefore we agree that ivabradine should only be considered in patients in whom β -blocker therapy has been titrated to the maximally tolerated dose and who have a persistently elevated heart rate.

Heart rate and quality of life.

In patients with systolic heart failure, a low health-related quality of life is associated with increased rates of cardiovascular death or hospital admissions for heart failure. In SHIFT, the magnitude of heart rate reduction with added ivabradine (about 10 bpm) was associated with an improved quality of life compared with placebo ($P < 0.001$).^{[87],[88]} Results from the small, unblinded CARVIVA-HF study suggest that ivabradine alone or in combination with carvedilol is safe and effective for improving exercise capacity and quality of life in heart failure patients on optimized ACE-inhibitor therapy.^[89]

Registration of ivabradine in the european union.

On March 16, 2012, the European Union extended the indication of ivabradine to the treatment of chronic heart failure New York Heart Association (NYHA) classes II to IV with systolic dysfunction in patients in sinus rhythm whose heart rate is 75 bpm or more, in combination with standard therapy, including β -blockade, or when β -blockers are contraindicated or not tolerated.

Renin-angiotensin-aldosterone system inhibitors: ACE inhibitors, ARBs, and aldosterone blockade.

The key concept is that ACE inhibitors and β -blockers should be used or at least considered for use in all patients. They should be titrated upward to the doses used in clinical trials unless hypotension or symptoms such as dizziness manifest themselves. When an ACE inhibitor is introduced for the first time to a patient already receiving high-dose diuretics (and therefore with intense renin-angiotensin activation), the diuretic dose must first be reduced and care taken to minimize or avoid first-dose hypotension. When an ACE inhibitor is truly not tolerated because of, for example, severe coughing, first ensure that worsening heart failure is not the cause of the cough, preferably with a rechallenge after complete resolution of the cough, and then change to an ARB on the basis of three large trials (CHARM, Val-HeFT, and VALIANT, see Chapter 5, p. 201). Aldosterone blockade is now increasingly established as the next step to achieve dual RAAS inhibition. Pregnancy warnings against the use of all the RAAS blockers must be heeded.

Worsening renal function during renin-angiotensin system inhibition.

In an editorial, Konstam points out, "It is reasonable to conclude that inhibiting the RAS reduces GFR through a mechanism that does not convey an adverse prognosis," based on the SOLVD (Studies of Left Ventricular Dysfunction) study, in which early reduction in GFR was associated with increased mortality within the placebo group but not in the enalapril group.^[90] Greater survival benefit of enalapril versus placebo was observed in patients with early worsening of renal function, which suggests that "GFR reduction is a marker of greater RAS inhibitory effect with a resulting greater survival benefit." Thus modest reduction of GFR could be a marker of benefit rather than harm.

Aldosterone antagonism.

Spironolactone reduces mortality in post-AMI class III and IV patients otherwise optimally treated.^{[91],[92]}

Eplerenone.

Eplerenone causes less gynecomastia than spironolactone, yet with either agent added to ACE inhibition or ARB therapy, plasma potassium needs intense monitoring. The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) demonstrated that the addition of the low-dose mineralocorticoid receptor antagonist eplerenone to standard medical therapy in patients with AMI and heart failure with LV systolic dysfunction improved survival by 15%, with reductions in cardiovascular death, sudden death, and hospitalization for heart failure.^[92] In EPHESUS, the doses were eplerenone 25 mg daily for the first month and up-titrated to 50 mg/day, with careful potassium monitoring, and great caution in the presence of renal failure. The mechanisms whereby eplerenone confers benefit on long-term survival and cardiovascular outcomes are independent from early potassium-sparing or diuretic effects, suggesting that mineralocorticoid receptor antagonism provides cardiovascular protection beyond its diuretic and potassium-sparing properties.^[93]

EMPHASIS-HF trial.

In the EMPHASIS-HF trial eplerenone was compared with placebo in well-treated patients with post-MI systolic heart failure (mean ejection fraction 26%) and mild symptoms.^[94] Eplerenone reduced both the risk of all-cause death (HR 0.76, CI 0.62-0.93; P = 0.008) and the risk of hospitalization (HR 0.77; CI 0.76-0.88; P < 0.001) while carefully monitoring the serum potassium level (see Chapter 5, p. 159). Additionally, the incidence of new-onset atrial fibrillation or flutter was reduced.^[95] Can eplerenone safely be given in post-MI heart failure without impairing renal function in heart failure with mild renal impairment? Despite a modest early decline in estimated glomerular filtration rate, eplerenone retained its prognostic benefits.^[96]

The role of ARBs.

ACE inhibitors are generally considered superior to ARBs for patients with CHF and LV systolic dysfunction (ELITE II, OPTIMAAL), and cost and length of clinical experience also favors ACE inhibitors. However, for ACE inhibitor-intolerant patients, there is strong evidence for an ARB, such as valsartan in the Val-HeFT trial,^[97] and candesartan.^[98] There is also strong evidence that the trial-tested ARB, candesartan, can be used in CHF patients who remain symptomatic on standard therapy such as ACE inhibitors and β -blockers in patients.^[99]

Which RAAS blockers and when?

There are now at least three ways in which the renin-angiotensin-aldosterone pathway may be inhibited: an ACE inhibitor, an ARB or aldosterone blockade, or various combinations of these. β -blockade also indirectly blocks the system. Which combination of drugs is best for which patient remains uncertain, as discussed in Chapter 5. The most difficult question relates to a patient already treated with diuretics, an ACE inhibitor, and a β -blocker. Should an ARB, an aldosterone antagonist, or both be added? Given that all three of the major outcomes trials with mineralocorticoid receptor antagonists (RALES, EPHESUS, EMPHASIS) demonstrated improved survival, the overall data and cost considerations usually decide in favor of aldosterone blockade. There is now emerging evidence for “quadruple therapy” (i.e., an ACE inhibitor, a β -blocker, spironolactone, and an ARB might benefit some carefully selected patients, but renal dysfunction and hyperkalemia must be strictly monitored). In addition, in self-identified black patients, isosorbide-hydralazine demonstrated significant reductions in all-cause mortality.^[100]

Phosphodiesterase-5 inhibitors.

PDE-5 inhibitors, best known for improving erectile function, also vasodilate the pulmonary and systemic vasculature (see Fig. 6-6). Initial evidence suggests that PDE-5 inhibitors benefit patients with CHF and secondary pulmonary hypertension (PH). “Cumulative data indicate that inhibition of PDE-5 is a promising approach for the treatment of ventricular remodeling induced by pressure or volume overload and heart failure.”^[101] In seven small trials on CHF, on a total of 199 patients, there were consistent improvements in measures such as the cardiac index.^[102] In one of the trials depression score decreased and quality of life improved. However, there are no large-scale, long-term placebo-controlled trials.

Digoxin.

Digoxin, as considered in detail later in this chapter, is no longer regarded as an essential drug but rather an optional choice, only carefully and selectively given in lower doses than before, on the grounds that it may give symptomatic improvement. Its many drug interactions and contradictions also limit its use. To achieve heart rate reduction beyond that obtained by β -blockade, ivabradine is a safer choice.^[103]

Antiarrhythmics.

Antiarrhythmics may be required. Ventricular tachyarrhythmias are a major cause of fatalities in CHF. It is important to avoid predisposing factors such as hypokalemia, digoxin excess, or chronic use of PDE inhibitors. Class I agents should be avoided. Long-term amiodarone may be considered in a low dose, and where there are facilities and there are good indications, an ICD may be chosen (see Fig. 8-16). Atrial fibrillation is a common and serious problem, and requires one of two policies: either conversion to sinus rhythm and thereafter probably low-dose amiodarone, or rate control both at rest and during exercise (see Fig. 8-13). The AF-CHF trial demonstrated that a rhythm-control strategy or the presence of sinus rhythm were not associated with better outcomes in 1376 patients with atrial fibrillation and CHF,^[104] so many clinicians opt for a rate-control strategy. β -blockers, digoxin, and amiodarone are commonly used for these effects, whereas CCBs are relatively contraindicated because of their negative inotropic properties.

Short-term inotropic support.

Short-term inotropic support by sympathomimetics or inotropic dilators cannot be lightly undertaken. Yet milrinone or others may give dramatic symptomatic relief as a rescue operation, when inotropic support is essential. In patients with exacerbation of heart failure, and not needing urgent inotropic or pressor support, there may be modest benefit at the risk of adverse effects.

Vasodilator therapy.

In patients who remain symptomatic despite full therapy (diuretics, ACE inhibitors, β -blockers, spironolactone, ARBs, and probably digoxin) isosorbide dinitrate with hydralazine is worth trying. The FDA approved the combination of isosorbide dinitrate and hydralazine as add-on treatment for CHF in self-defined black subjects, largely on the basis of the 43% reduction in all-cause mortality among the 1050 self-identified blacks in the A-HeFT trial.^[100] Whether this combination in addition to standard therapy is effective in non-black populations has not been directly tested. *Hydralazine* is predominantly an arteriolar dilator probably acting as a vascular potassium channel opener. Hydralazine may potentiate nitrates by retarding the development of nitrate tolerance (see Fig. 2-7). The role of hydralazine alone in heart failure patients already treated by diuretics, ACE inhibitors, and other effective agents is not clear and not recommended.

Novel drugs.

Aquaretics or “vaptans” antagonize the vasopressin type 2 receptors in the kidney, thereby promoting free water clearance and lessening hyponatremia (see Fig. 4-5). In the long term, their use has been relatively disappointing (see Chapter 4, p. 107). *Perhexiline* acts metabolically to inhibit adverse myocardial fatty acid oxidation, but requires monitoring of blood levels to avoid hepatic or neural toxicity.^[105] Perhexiline may be particularly useful in patients with both refractory angina and heart failure.^[106] *Trimetazidine*, another partial fatty acid inhibitor that has minimal side effects and is available in some European countries, improves LV function and insulin sensitivity in idiopathic dilated or ischemic cardiomyopathy.^[107] Other reports show benefit in ischemic or diabetic cardiomyopathy,^[108] and a recent metaanalysis of 884 patients suggested beneficial effects on multiple clinical outcomes, including LV remodeling.^[109] *Sildenafil*, already erotically famous, is emerging under another guise as a possible aid to the failing myocardium by increasing cyclic GMP (see Fig. 6-6). *Pentoxifylline* is a complex agent that decreases the synthesis of tumor necrosis factor- α (TNF α) and improves the ejection fraction, yet it also has PDE activity and outcome data are missing.^[110] Vasopressin (ADH) antagonists are logical, but the results with *tolvaptan* in the EVEREST trial were disappointing in terms of their ability to improve long-term outcomes.^{[62],[63]} Many other agents to improve cardiac performance are under investigation as well.^[41] Of these prospects, the only agents that are already available and licensed, albeit not for use in CHF, are tolvaptan, pentoxifylline, and sildenafil. Those that should work but have been disappointing include (1) endothelin (ET) antagonists, which should unload the heart by vasodilation and improve coronary endothelial integrity; and (2) cytokine antagonists, including etanercept that decoys TNF α from its receptor.

Gene therapy.

Impaired contraction is now firmly established as a key feature of advanced heart failure, so that the current interest in upregulation of the cardiac sarcoendoplasmic calcium-transporting ATPase (SERCA2a) is clinically relevant (see Fig. 6-8).^[111] SERCA2a has been upregulated in human heart failure by adeno-associated virus type 1/SERCA transfer delivered by antegrade epicardial coronary artery infusion with clear benefit over 12 months in a small phase 2 human trial.^[112] Furthermore, there is now the theoretical possibility of molecular upregulation of SERCA2 by SUMOylation, in which SUMO represents the small ubiquitin-related modifier type 1.^[113]

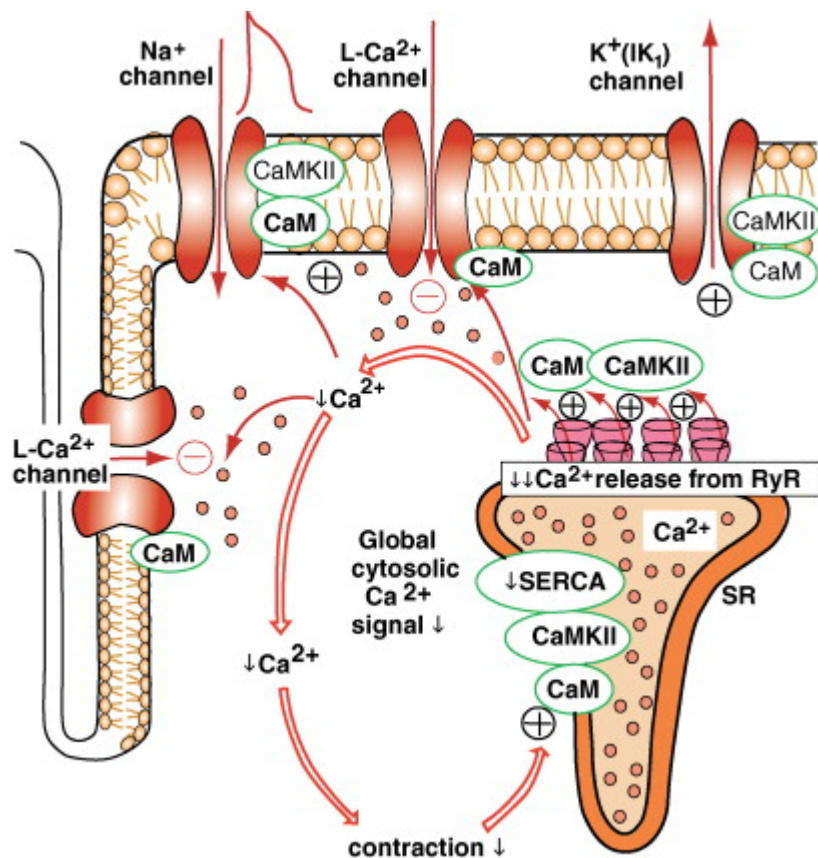


Figure 6-8 Gene therapy to promote intracellular calcium ion movements in heart failure. Sites of action. The regulation of Ca²⁺ changes in heart failure from the normal pattern (see Fig. 1-1) to a diminished and restricted flow of Ca²⁺. Gene therapy, still in early development, aims to upregulate the activity of sarcoplasmic endoplasmic reticulum calcium-ATPase (SERCA), the key enzyme in regulation of Ca²⁺ uptake into the sarcoplasmic reticulum (SR), hence increasing release of Ca²⁺ from the SR into the cytosol via the ryanodine receptors (RyR). The overall effect is to enhance the Ca²⁺ signal to contraction. Upregulation of SERCA by gene therapy *would not* directly correct other ion abnormalities, such as diminished Ca²⁺ entry via the L-calcium channel, the enhanced entry of sodium ions, and increased potassium ion loss. Thus far there is no specific therapy to correct these ionic abnormalities. For acute heart failure, the catecholamine inotropes (see Fig. 6-4) and inodilators (see Fig. 6-6) increase the depleted intracellular Ca²⁺ stores. For chronic HF, β -blockers (see Figs. 1-7 and 1-8) and ivabradine act by totally different ionic currents to reduce calcium ion influx, therefore being additive in effects (see Fig. 8-4). Digoxin also acts differently to inhibit the sodium-potassium pump followed by sodium-Ca²⁺ exchange to increase intracellular Ca²⁺, thus indirectly promoting contractility with an added and separate vagomimetic effect (see Fig. 6-11).

(Figure © L.H. Opie, 2012.)

Stem cell therapy.

An initial study suggests that intracoronary infusion of autologous cardiac stem cells improves LV systolic function and reduces infarct size in patients with heart failure after MI,^[114] and another study using intracoronary autologous cardiosphere-derived cells demonstrated reductions in scar mass, increases in viable heart mass and regional contractility, and regional systolic wall thickening, but no associated changes in ventricular volumes.^[115] Additional studies with mesenchymal precursor cells have also been encouraging, so that further larger, phase 2 studies with these different approaches will follow.

Therapy of anemia: Erythropoietin-stimulating agents.

Chronic heart failure is often accompanied by anemia, which may be a new therapeutic target in heart failure. Intravenous iron, erythropoietin, and erythropoietin-stimulating agents such as darbepoetin alfa can increase hemoglobin, but that in itself gives no clinical benefit.^[116] In some, ACE inhibition contributes or even causes the anemia (see Chapter 5, p. 133). In the TREAT STUDY on 4038 patients with diabetes mellitus, chronic kidney disease, and anemia randomized to receive darbepoetin alfa or placebo, the twofold increase in stroke with darbepoetin alfa could not be explained.^[117] The FDA now has boxed warnings on

the erythropoietin-stimulating agents pointing out the dangers, although allowing initiation of treatment if hemoglobin is less than 10 g/dL, with focus on transfusion avoidance, corresponding to the originally demonstrated benefit approved in 1989. Nonetheless, one trial is underway with darbepoetin alfa to test the hypothesis that the expected outcome benefit of anemia correction by this agent in heart failure would outweigh safety concerns.^[118]

Iron hemostasis and health-related quality of life.

Surprisingly, from the patients' point of view, it is not only the hemoglobin that matters. More positive are the findings from the preliminary, relatively small, 459-patient FAIR-HF study that intravenous ferric carboxymaltose given to patients with chronic heart failure and iron deficiency, with or without anemia, improves symptoms, functional capacity, and quality of life with an acceptable side-effect profile.^[119] Intravenous ferric carboxymaltose significantly improved health-related quality of life after 4 weeks and throughout the study period. Importantly, the benefits were independent of anemia status.^[120]

Cardiac resynchronization therapy and implantable cardioverter defibrillators.

CRT (biventricular pacing) and ICDs are being increasingly used in patients with heart failure. Both devices have reduced mortality in large clinical trials or in metaanalyses. The precise indications are still controversial. CRT is usually considered when there is QRS prolongation as a sign of impaired intraventricular conduction. These treatments may be life-saving but are expensive, which raises serious problems in relation to national medical budgets.

Cardiac surgery.

Cardiac surgery must be considered when valve defects are present, there is clear evidence of myocardial ischemia, or a remodeling procedure is indicated. The utility of ventricular reconstruction surgery remains debated, although the results of the hypothesis 2 component of the STICH trial suggests that this role may be very limited.^[121] The hypothesis 1 component of STICH also suggested that there was no significant difference between medical therapy alone and medical therapy plus coronary artery bypass graft (CABG) with respect to death from any cause in patients with coronary artery disease and LV dysfunction.^[122] Furthermore, the assessment of myocardial viability did not identify patients with a differential survival benefit from CABG, as compared with medical therapy alone.^[123]

Last resorts.

Severe heart failure refractory to furosemide may benefit from *extracorporeal ultrafiltration* for the removal of intravascular fluid.^[124] *Cardiac transplantation* or *destination therapy with an LVAD* are measures of last resort, although better outcomes are emerging with improved technologies^{[125],[126]} and better patient selection.^[127] The number of transplants is falling partly because of the lack of donors and the improvement of medical and device therapy. The indications are now more stringent than previously. There are no controlled trials of transplantation. Mechanical assist devices are also being considered for lifetime treatment.

Maximal heart failure therapy summarized

As the severity of heart failure progresses, so does the need for established and novel therapies (Fig. 6-9). Fully fledged heart disease is a complex phenomenon, starting with the heart and involving the lungs, the kidneys, and the peripheral vasculature (Fig. 6-10). Maximal therapy includes both the established therapies as shown on the top left of Fig. 6-10, with the novel therapies below. Of the latter, the I_f blocker ivabradine is approved for addition to β -blockade in the European Union for patients with a persistent tachycardia. Specific drugs are required to act on pulmonary edema (see "Acute Heart Failure" earlier in chapter), the kidneys, and the peripheral arteries. For the latter two sites of therapy, RAAS blockade remains fundamental.

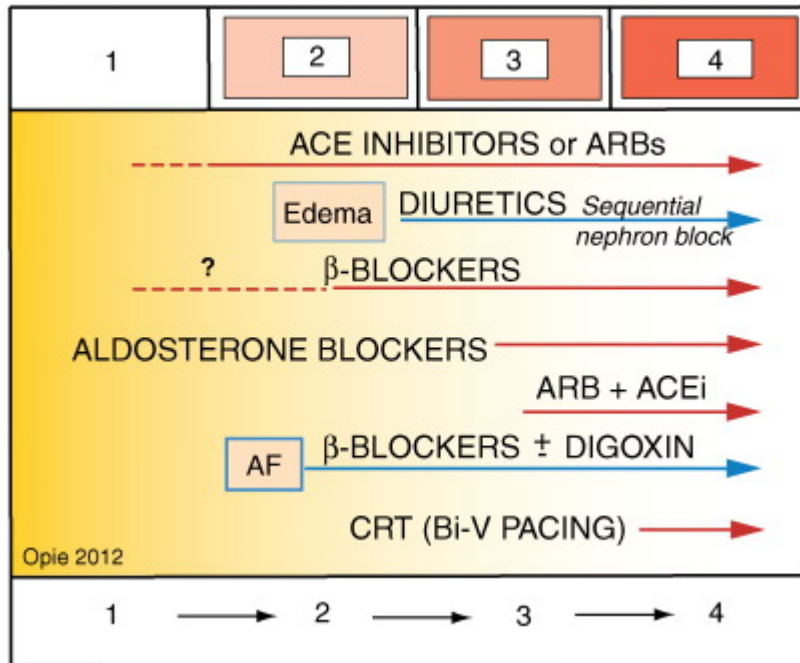
Progressive chronic heart failure, NYHA classes

Figure 6-9 Schematic therapy of progressive chronic heart failure. Note early use of angiotensin converting enzyme (ACE) inhibitors, and increasingly early use of β -blockers. The role of diuretics is fundamental in relief of edema and fluid retention, using the principle of sequential nephron block. Angiotensin receptor blocker (ARB) + ACE inhibitor (ACEi): the combination of these agents was used in some trials with benefit. However, this combination is controversial. Cardiac resynchronization therapy (CRT), also called *biventricular* (Bi-V) pacing, is used later. AF, Atrial fibrillation; NYHA, New York Heart Association class of severity of heart failure.

(Figure © L.H. Opie, 2012.)

MAXIMAL THERAPY FOR SEVERE CHF

Opie 2012

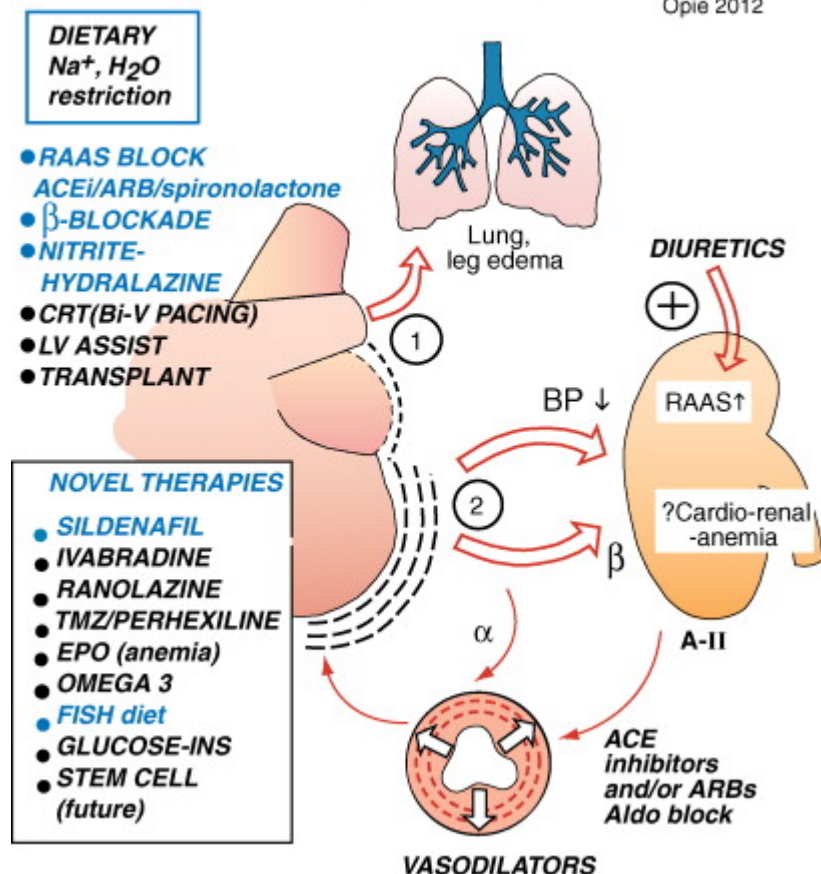


Figure 6-10 Principles of maximum therapy for congestive heart failure (CHF). Diuretics are given for back pressure into the lungs with edema (1) yet stimulate the renin-angiotensin-aldosterone system (RAAS). Poor left ventricular (LV) function also activates this system (2) by a low blood pressure with decreased renal perfusion or by reflex β-adrenergic (β) baroreceptor activation. Vasoconstriction results from formation of angiotensin-II (A-II) or from α-adrenergic activity. Logically, angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) are an integral part of the therapy, as are β-blockers. Aldosterone (Aldo) blockers are also essential. Among other therapies, ivabradine is the best tested. Nitrate-hydralazine benefited self-declared black patients in the United States, but may well relieve vasoconstriction in others. Trimetazidine (TMZ) and perhexiline inhibit myocardial fatty acid oxidation to improve ejection fraction. Sildenafil should help by increasing cyclic guanosine monophosphate (see Fig. 6-7). Biventricular pacing (Bi-V), also called *cardiac resynchronization therapy* (CRT), is especially used when there is delayed ventricular conduction (long QRS). LV assist devices are regarded as a bridge to transplantation. Stem cells are for the future. (Figure © L,H, Opie, 2012.)

Digoxin in perspective

The combined inotropic-bradycardic actions of digoxin (Fig. 6-11) are unique when compared with the many sympathomimetic inotropes that all tend to cause tachycardia. Besides its weak positive inotropic effect, it slows the ventricular rate, which allows better ventricular filling in CHF, especially with atrial fibrillation. Digoxin also decreases the sympathetic drive generated by the failing circulation, which provides a rationale for its use in CHF in sinus rhythm. Nonetheless, this use is now controversial, especially because a trial on 6800 patients failed to show any mortality benefit for digoxin, despite the absence of treatment with β-blockers, aldosterone antagonists, and devices.^[128] Consequently, its use in sinus rhythm remains optional and controversial with some strong arguments against its use.^[129] The optimal use of digoxin requires a thorough knowledge of the multiple factors governing its efficacy and toxicity, including numerous drug interactions. Because the effects of digoxin in the acutely ill patient with hypoxia and electrolyte disturbances are often difficult to predict and because there is a lack of evidence of efficacy, digoxin is now very seldom justified in acute heart failure and is much less used in chronic heart failure. Nonetheless it remains the only drug for chronic heart failure that inhibits the sodium pump.

INOTROPIC, VAGAL AND SYMPATHETIC EFFECTS OF DIGOXIN

Opie 2012

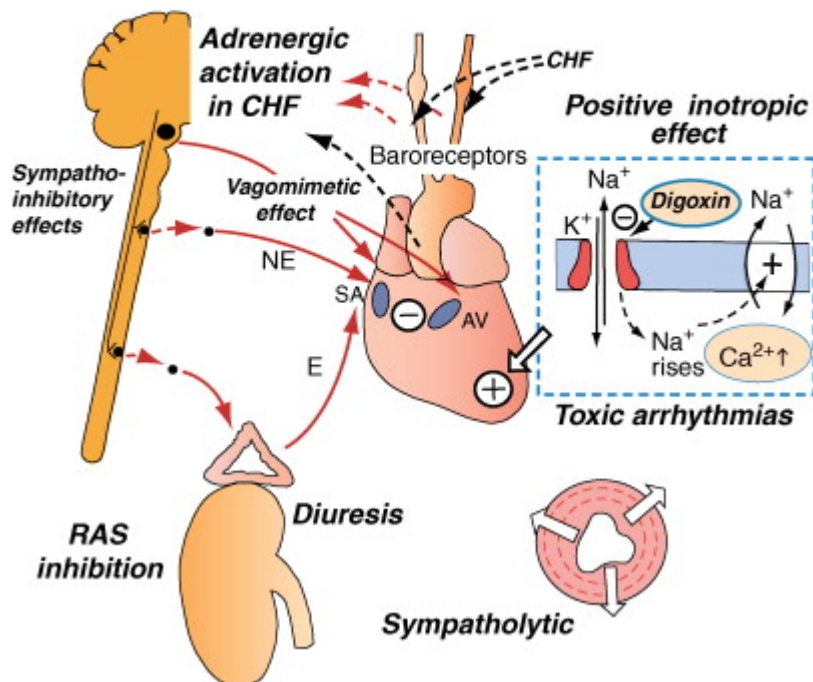


Figure 6-11 Digoxin has both neural and myocardial cellular effects. The inotropic effect of digoxin is due to inhibition of the sodium pump in myocardial cells. Slowing of the heart rate and inhibition of the atrioventricular (AV) node by vagal stimulation and the decreased sympathetic nerve discharge are important therapeutic benefits. Toxic arrhythmias are less well understood, but may be caused by calcium-dependent afterpotentials. CHF, Congestive heart failure; E, epinephrine; NE, norepinephrine; RAS, renin-angiotensin system; SA, sinoatrial. (Figure © L.H. Opie, 2012.)

Sodium pump inhibition.

Sodium pump inhibition explains the myocardial cellular effect of digitalis. As the sodium pump (Na/K-ATPase) is inhibited, there is a transient increase in intracellular sodium close to the sarcolemma, which in turn promotes calcium influx by the sodium-calcium exchange mechanism to enhance myocardial contractility (Fig. 6-11), with arrhythmogenic risk. However, digoxin is still inotropic at lower doses and blood levels than previously standard.^[130-132]

Direct calcium uptake.

Digoxin toxicity, studied with digitoxin, promotes calcium entry into heart cells through new transmembrane calcium channels.^[133]

Autonomic and renin-angiotensin effects.

Sinus slowing and atrioventricular (AV) nodal inhibition results from *parasympathetic activation*. A modest direct depression of nodal tissue may account for those effects of digoxin still found after vagal blockade. The action of digoxin on AV conduction, which it slows, and on the AV refractory period, which it prolongs, is primarily dependent on increased vagal tone, rather than the direct effect of digoxin. Part of the toxic symptoms of digitalis may be explained by parasympathomimetic effects, such as nausea, vomiting, and anorexia. *Sympathetic inhibition* may play an important role in the effects of digitalis in CHF. Digitalis inhibits sympathetic nerve discharge, an effect that occurs before any observed hemodynamic changes.^[131] *Renin release* from the kidney is inhibited because digoxin decreases the activity of the renal sodium pump with a natriuretic effect. Less renin release should lead to vasodilation to help offset the direct vasoconstrictor

mechanism of digoxin.

Pharmacokinetics of digoxin (table 6-6).

The serum half-life of digoxin is 1.5 days. Approximately one third of the body stores are lost daily, mostly as unchanged digoxin by the kidneys. Approximately 30% is excreted by nonrenal routes (stools, hepatic metabolism) in those with normal renal function. In digitalized subjects, approximately half of the digoxin is bound to skeletal muscle receptors accounting (with blood) for most of the volume of distribution. The "fit" between digitalis and the receptor is much less "tight" for skeletal muscle than for the myocardium, which remains the major site of action. Multiple pharmacokinetic factors influence the blood level obtained with a given dose of digoxin (see Tables 6-6 and 6-7 in *Drugs for the Heart*, 7th edition) and the sensitivity to digoxin (Table 6-7). In *renal impairment*, excretion is decreased and the maintenance dose is lower. The loading dose may also be lower (next section).

Table 6-6 -- Digoxin Pharmacokinetics

1.	Rapid absorption of 75% of oral dose; the rest is inactivated in lower gut to digoxin reduction products by bacteria.
2.	Circulates in blood, unbound to plasma proteins; previous "therapeutic level" 1-2 ng/mL, current ideal level 0.5-1 ng/mL* (0.65-1.3 nmol/L); blood half-life approximately 36 h.
3.	Binds to tissue receptors in heart and skeletal muscle.
4.	Lipid-soluble; brain penetration.
5.	Most of absorbed digoxin excreted unchanged in urine (tubular excretion and glomerular filtration). Approximately 30% undergoes nonrenal clearance, more in renal failure.
6.	In chronic renal failure, reduced volume of distribution.
7.	With small lean body mass, reduced total binding to skeletal muscle.

* Optimal range 0.5 to 0.8 ng/mL in men.[136]

Table 6-7 -- Factors Altering Sensitivity to Digoxin at Apparently Therapeutic Levels

Physiologic effects
Enhanced vagal tone (increased digoxin effect on SA and AV nodes)
Enhanced sympathetic tone (opposite to vagal effect)
Systemic factors or disorders
Renal failure (reduced volume of distribution and excretion)
Low lean body mass (reduced binding to skeletal muscle)
Chronic pulmonary disease (hypoxia, acid-base changes)
Myxedema (? prolonged half-life)
Acute hypoxemia (sensitizes to digitalis arrhythmias)
Electrolyte disorders
Hypokalemia (most common; sensitizes to toxic effects)
Hyperkalemia (protects from digitalis arrhythmias)
Hypomagnesemia (caused by chronic diuretics; sensitizes to toxic effects)
Hypercalcemia (increases sensitivity to digitalis)
Hypocalcemia (decreases sensitivity)
Cardiac disorders
Acute myocardial infarction (may cause increased sensitivity)
Acute rheumatic or viral carditis (danger of conduction block)
Thyrotoxic heart disease (decreased sensitivity)
Concomitant drug therapy
Diuretics with K ⁺ loss (increased sensitivity via hypokalemia)

Drugs with added effects on SA or AV nodes (verapamil, diltiazem, β -blockers, clonidine, methyldopa, or amiodarone)

AV, Atrioventricular; SA, sinoatrial.

Digoxin use: Changes in clinical practice.

(1) *Chronic atrial fibrillation without overt CHF* may now be the condition for which digoxin is probably most often used. Unfortunately even when used by cardiologists in well-organized trial studies for atrial fibrillation, as in PALLAS, the mean levels were in the toxic range and could, hypothetically, have contributed to a higher incidence of heart failure.^[134] Digoxin may be combined with verapamil, diltiazem, or β -blocking drugs to control the ventricular rate during exercise. However, note that the optimal heart rate remains moot. Note the verapamil-digoxin interaction whereby verapamil decreases nonrenal clearance. (2) In *chronic atrial fibrillation with heart failure* there are no good outcome studies^[129] so that its dosage and effects are still judged clinically. A logical combination is with a β -blocker that not only slows the ventricular rate but improves exercise tolerance and the ejection fraction.^[135] Note the absence of any hard event outcome data. (3) In *CHF with sinus rhythm* the limited benefits found in the large DIG trial,^{[128].}^[136] the very narrow therapeutic-toxic window,^[130] and numerous drug interactions (see Tables 6-6 and 6-7 in *Drugs for the Heart*, 7th edition) have cast major doubts on the ideal dose and blood levels. *These problems have relegated digoxin to an optional and potentially dangerous extra in the management of CHF*, if not carefully given in lower doses than before. In 2009 the American College of Cardiology and AHA gave digitalis a level of evidence B, but this appears not to be based on any current outcome trial. Digitalis can be beneficial in patients with current or prior symptoms of heart failure and reduced LV ejection fraction to decrease hospitalizations for heart failure.^[137] Note that the hard data for the benefits of heart rate reduction in heart failure are strong for ivabradine (see page 195) and weak for digoxin.

Digoxin for ambulatory patients.

Going back to data based on the DIG trial 1997, in ambulatory patients with chronic heart failure and low serum digoxin concentrations (SDCs), mortality and hospitalizations were reduced.^[138] Low-dose digoxin ($< \text{or} = 0.125 \text{ mg/day}$) was the strongest independent predictor of low SDC (adjusted odds ratio, 2.07; 95% CI 1.54-2.80). Thus digoxin in a lower dose might be best for those already on it, or for those who cannot access effective modern agents.

Digoxin not for advanced heart failure.

In patients with advanced heart failure referred for cardiac transplantation and otherwise optimally treated, digoxin was associated with a higher risk for the primary outcomes (chiefly death) with a hazard ratio 2.28 ($p < 0.001$). There was deterioration in major outcomes (combined death, urgent transplant or insertion of LV assist device) and increased hospitalization rates.^[139]

Doses and blood levels of digoxin.

There is general agreement that the therapeutic-toxic window of digoxin is narrow. Previously, the ideal blood level was pragmatically regarded as 1-2 ng/mL (1.3-2.6 nmol/L). Currently lower doses and lower blood levels are finding strong spokesmen. Supportive data come from a retrospective analysis of the large DIG trial on 3782 heart failure patients followed up for 3 years.^[136] All-cause mortality was modestly decreased, albeit by only 6% in the tertile with digoxin levels in the previously "low" range, 0.5 to 0.8 ng/mL or 0.6 to 1 nmol/L. The next tertile of digoxin levels (0.9-1.1 ng/mL) had no effect on mortality, whereas higher levels (1.2 ng/mL or more) were associated with a mortality increase of 12%.^[136] *The hypothesis, based on the "old" trials, is that digoxin has bidirectional effects on mortality, with the "turn around" level being approximately 1 ng/mL,*^[130] giving a practical therapeutic range of 0.5 to 1.0 ng/mL (Fig. 6-12).

PRESENT and PAST TOXIC DIGOXIN LEVELS

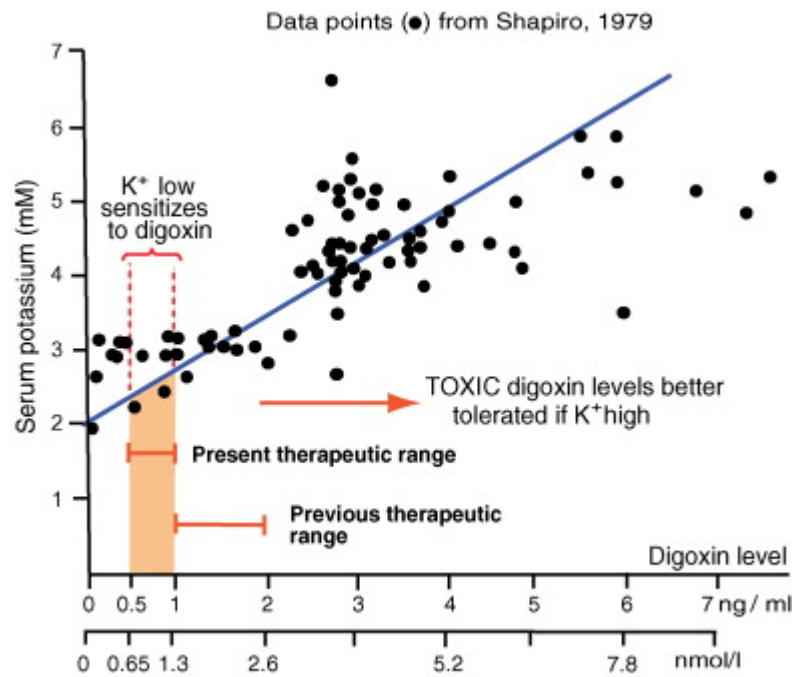


Figure 6-12 Possible therapeutic and toxic serum digoxin levels. As the serum potassium falls, the heart is sensitized to the arrhythmias of digitalis toxicity. Conversely, as the serum potassium rises, a higher serum digoxin level is tolerated. Note current lower “therapeutic” levels of digoxin. There are no good prospective data linking digoxin levels to outcome. (Potassium data modified from Shapiro W. *Am J Cardiol* 1978;41:852–859.)

Digitalization.

First check renal function and then consider the age of the patient. Currently the trend is toward lower digoxin dose, commonly initiated at 0.25 mg per day, followed by 0.125 mg daily, and even lower doses if the patient is older than 70 years old or in renal impairment.^[26] *Blood digoxin levels* are still valuable to allow for variable GI absorption, variable cardiac responses, and possible drug interactions. Steady-state plasma and tissue concentrations are achieved in 5 to 7 days.

Digoxin contraindications.

Contraindications include *hypertrophic obstructive cardiomyopathy*, some cases of *Wolff-Parkinson-White syndrome* with atrial fibrillation (see Fig. 8-14), *significant AV nodal heart block*, and *diastolic dysfunction*. Relative contraindications are *renal failure* and *older age* (reduce doses).

Digoxin in women.

In the DIG trial, only 22% of participants were women, in whom there was an unexplained increased 23% risk of all-cause mortality.^[140] Speculatively, the authors thought that there could be a renal interaction with hormone replacement therapy, commonly used at that time.

Digoxin and breast cancer.

Two studies show an increased risk of breast cancer with digoxin use in women. The larger study relates to use at any time,^[141] and the other to continuous use for at least 2 years and to invasive cancer.^[142]

Digoxin in older adults.

Decreased skeletal muscle, lean body mass, and renal function increase digoxin levels (see Table 6-7).

Digoxin half-life may be prolonged up to 73 hours, depending on renal function. The *digoxin dose* is often lower than 0.125 mg daily, such as 0.125 mg every second day. The exact dose required can be calculated from the total body weight, serum creatinine, age, presence of heart failure, concomitant CCBs (verapamil, diltiazem, or nifedipine), gender, and trough digoxin concentration.^[143]

Drug interactions.

The most recent interaction is a potentially lethal interaction with dronedarone.^[134] The *verapamil-digoxin* interaction is also important, with blood digoxin levels rising by approximately 50% to 75%. *Amiodarone* and *propafenone* (for Amiodarone see p. 289; for propafenone see p. 284) also elevate serum digoxin levels. *Diuretics* may induce hypokalemia, which (1) sensitizes the heart to digoxin toxicity (see Fig. 6-12), and (2) shuts off the tubular secretion of digoxin when the plasma potassium falls to below 2-3 mEq/L.

Digoxin toxicity.

In April 2008, 800 million digoxin tablets (Digitek) were recalled by the manufacturer as possibly containing double the labeled amount of drug.^[144] The typical patient with digoxin toxicity (see Table 6-7) is an older adult woman with advanced heart disease and bradycardia, and abnormal renal function.^[145] Hypokalemia is common (see Fig. 6-10). Digitalis toxicity should be considered in any patient receiving digoxin who presents with new GI, ocular, or central nervous system complaints, or new arrhythmia or AV conduction disturbance. The *cellular mechanism* of toxicity includes (1) intracellular calcium overload that predisposes to calcium-dependent delayed afterdepolarizations (see Fig. 6-11); (2) excess vagal stimulation, predisposing to sinus bradycardia and AV block; and (3) an added "direct" depressive effect of digoxin on nodal tissue.

Treatment of digoxin toxicity.

The diagnosis of digoxin toxicity is confirmed if the digoxin blood level is inappropriately high for the patient in the presence of suspicious clinical features. With only suggestive symptoms, *withdrawal of digoxin* is sufficient while awaiting confirmation by elevated plasma levels. With dangerous arrhythmias and a low plasma potassium, potassium chloride may be infused intravenously very cautiously as 30 to 40 mEq in 20 to 50 mL of saline at 0.5 to 1 mEq/min into a large vein through a plastic catheter (infiltration of potassium solution can cause tissue necrosis and infusion into small veins causes local irritation and pain). *Phenytoin* reverses high-degree AV block, possibly acting centrally. *Dose:* Stop β -blockers and any drugs elevating the blood digoxin levels (verapamil). Because of its very long half-life, don't stop amiodarone. *Oral potassium* (4 to 6 g potassium chloride, 50 to 80 mEq) may be given orally in divided doses when arrhythmias are not urgent (e.g., premature ventricular contractions). Potassium is contraindicated if AV conduction block or hyperkalemia are present, because potassium further increases AV block. *Activated charcoal* (50 to 100 g) enhances GI clearance of digoxin. *Cholestyramine* has a similar but less powerful effect.

Digoxin-specific antibodies (digibind).

Digoxin-specific antibodies (Digibind) can be strikingly effective therapy for life-threatening digoxin intoxication, especially when there is severe ventricular tachycardia or significant hyperkalemia (>5.5 mEq/L). To calculate doses, work out the total body digoxin load from the blood level; each vial binds approximately 0.5 mg of digoxin.

Digoxin: Summary.

Digoxin is an extremely complex drug with unique properties and is increasingly seen as having a limited role that requires expert initiation and supervision.

Heart failure with preserved systolic function: Diastolic heart failure

Definitions.

In standard descriptions of heart failure therapy, it is often forgotten that approximately half of those with clinical heart failure are not suffering from predominant heart failure with reduced systolic function (HFrEF), but rather systolic function is relatively preserved and diastolic failure dominates. The current term for this situation is *heart failure with preserved ejection fraction* (HF-Preserved EF, or HFpEF), which, however,

gives no mechanistic insight. The definition of preserved ejection fraction varies, often being equal to or more than 50%,^[146] but different cut-off values are taken in various studies, such as 45%,^[147] 40%,^[148] or even 35%.^[149] Overall, the condition is serious, with a long-term prognosis very similar to that of systolic failure.^{[146],[150]} Besides the problem of the differing levels of ejection fraction for diagnosis, there are no accepted mechanistic explanations. Those proposed include increased muscle stiffness (as, for example, from fibrosis) with greater sensitivity to volume overload, and LV remodeling and dilation with volume-dependent increased LV filling pressures.^[151]

The closely related condition of *diastolic heart failure* is a syndrome with signs and symptoms of heart failure, which in addition has echocardiographic evidence of LV diastolic dysfunction,^[152] thus being more precise. For example, in a subset of patients with HFpEF in the CHARM-preserved study with a mean ejection fraction of 50%, one-third did not have objective diastolic dysfunction, suggesting a deficiency in either the specificity of the clinical criteria or the sensitivity of the echocardiographic criteria, or some combination. Moderate and severe diastolic dysfunction were important predictors of adverse outcome in less than one half of these patients.^[153] Conversely, diastolic dysfunction even in the absence of heart failure is also a serious condition. It progresses to a combined incidence of mortality and overt heart failure of 20% over 3 years.^[152] To diagnose diastolic dysfunction requires expert echocardiography, including at least mitral valve and pulmonary vein inflow pattern by pulse-wave Doppler and mitral annular velocities by tissue Doppler imaging.

The pathophysiologic characteristics of HFpEF is incompletely understood. In patients with clinical diastolic heart failure (DHF), there were significant abnormalities in LV relaxation and increased LV chamber stiffness as assessed by invasive hemodynamics and echocardiography.^[154] Magnetic resonance imaging (MRI) studies confirm that concentric geometry and hypertrophy resulting from LV systolic pressure overload as in hypertension is one underlying cause of left ventricular hypertrophy with preserved ejection fraction.^[155] In a group of older adult patients with concentric hypertrophy with heart failure at the start, only 25% developed LV systolic dysfunction over 7 years.^[156] Those with heart failure and preserved ejection fractions have more noncardiac comorbidities (four on average) and *more* noncardiovascular hospitalizations and fewer heart failure–related hospitalizations than those with reduced ejection fraction.^[157] Non–heart failure hospitalizations, which dominate, are three times greater in patients with HFpEF. The strong implication is that all these comorbidities, which may be the chief problem, need assessment and therapy.^[157]

Incidence.

HFpEF is the most common form of HF in the population, being dominant among older adults.^[157] HFpEF is more common in older adults and in women and is becoming more common as the population ages.^[146] The major predisposing causes are obesity, hypertension, coronary artery disease, and diabetes.^{[146],[148],[150]} Obesity leading to hypertension and hypertensive heart failure is of particular importance in black patients.^[158] In those black patients presenting with hypertension, the mean LV ejection fraction was 55%, and diastolic dysfunction was echocardiographically diagnosed in 24%.^[159] The 10-year analysis from the Copenhagen Hospital Heart Failure study showed that among patients with a clinical diagnosis of heart failure, 61% had a preserved ejection fraction,^[160] but when the added requirement for heart failure diagnosis was an elevated N-terminal pro B-type natriuretic peptide (NT-proBNP), only 29% had “true” HFpEF.

Therapy.

The underlying cause should be vigorously treated (control hypertension, prevent myocardial ischemia, reduce LV hypertrophy) and particular attention paid to the avoidance of tachycardia and the control or prevention of atrial fibrillation. Fluid retention is treated with diuretics, but then what? Treatment strategies for HFpEF remain unproven despite several large-scale trials. Holland et al. undertook a metaanalysis of the effects of pharmacologic interventions on exercise capacity, diastolic function, and mortality in 20 randomized controlled trials, with β -blockers (7); ACE inhibitors (8); CCBs (2); and one each of statins, diuretics, and ACE inhibitor–ARBs.^[161] They also analyzed 12 observational studies. Exercise tolerance was improved ($n = 183$; CI: 27.3 to 75.7; $p < 0.001$), but not the early-to-late diastolic filling ratio, an index of diastolic dysfunction. All-cause mortality was unchanged.

Specific trials.

Angiotensin receptor blockers.

Candesartan was added in CHARM-Preserved,^[148] to prior therapy by diuretics (75%), β -blockers (56%), CCBs or other vasodilators (68%), or digoxin (28%), with prior ACE inhibition in only 19%. After a mean follow up of 3 years, only one combined secondary endpoint was positive, namely cardiovascular death, hospitalization for CHF, MI, or stroke ($p = 0.037$). Total mortality and total hospitalizations were unchanged. Using a new index of the efficacy of heart failure therapy, days alive and out of hospital, candesartan was better than placebo by 24.1 days over the length of the study ($P < 0.001$).^[162] In the I-PRESERVE trial, 4128 patients with heart failure and LV ejection fraction of 45% or more were randomized to *irbesartan* or placebo and followed for more than 4 years.^[163] There were no significant differences in the primary endpoint of all-cause mortality or cardiovascular hospitalizations (heart failure, MI, arrhythmia, or stroke) or any of the other prespecified outcomes. Paradoxically, *irbesartan* showed unexpected benefit in lower-risk patients with HFpEF.^[164] “Lower risk” was defined by the lower-range plasma concentrations of NPs, suggesting benefits of early, but not later, higher-risk stages of the disease. As this was a posthoc analysis, prospective studies are required to further investigate this potential benefit.

ACE inhibitors for HFpEF.

In the PEACE trial, 8290 apparently low-risk patients with stable coronary artery disease and preserved LV ejection fraction ($\geq 40\%$; mean 59%) were randomized to either *trandolapril* or placebo and followed for more than 6 years with no significant difference in death from cardiovascular causes, MI, or coronary revascularization between the treatments.^[165] Although these patients did not have HFpEF, there was an outcome benefit detected over 6 years, including reduced risk of cardiovascular death or heart failure in those subgroups initially identified by novel biomarkers.^[166] In contrast to previous results with other biomarkers such as NT-proBNP, elevated levels of two or three of these selected biomarkers (midregional pro-A-type natriuretic peptide, midregional proadrenomedullin, and C-terminal proendothelin-1) identified the patients at high risk. In this subset, only 14 patients would have to be treated for 6 years to prevent one cardiac death or hospitalization for heart failure. *Perindopril* was compared with placebo in the PEP-CHF trial in older adult subjects with a diagnosis of heart failure, treated with diuretics and an echocardiogram suggesting diastolic dysfunction and excluding substantial LV systolic dysfunction or valve disease.^[167] Although there was no significant difference in the primary endpoint of all-cause mortality or unplanned heart failure-related hospitalization, possibly attributable to high drop-out and cross-over to open label ACE inhibitor rates, there were trends at 1 year to improvements in hospitalization for heart failure, functional class, and 6-minute corridor walk test in patients treated with perindopril. Given these results and the beneficial effects of ACE inhibitors in other studies of cardiovascular disease (e.g. HOPE; EUROPA), we believe that ACE inhibitors should be considered as therapy in these patients, especially in the presence of other indications like hypertension.

B-blockade for HFpEF.

The effect of *nebivolol* on outcomes was compared with placebo in 2128 patients with a history of heart failure and a wide range of LV systolic function (LV ejection fraction $\geq 35\%$) in the SENIORS study.^[77] The primary endpoint of all-cause mortality or cardiovascular hospital admission was significantly improved by nebivolol, although mortality was statistically unchanged. Interestingly, there was no difference of note between the beneficial effect of nebivolol between patients with ejection fractions of less than or more than 35%, suggesting that there may have been an improvement in outcomes in patients with less severe LV dysfunction. Also note that the mean systolic BP in the preserved ejection fraction group was 145 mm Hg versus 135 mm Hg in the lower ejection fraction group,^[149] so that BP reduction might in part explain the positive result.

Role of aldosterone blockers.

Increasing evidence suggests that enhanced aldosterone signaling plays a key role in the onset and progression of HFpEF and in DHF. Aldosterone, a potent stimulator of myocardial and vascular fibrosis, may be a key mediator of heart failure progression in this population and is therefore an important therapeutic target. The effects of eplerenone were tested in a small, randomized, double-blind, placebo-controlled trial of only 44 patients with HFpEF.^[156] There were no changes in the 6-minute walk distance, the primary endpoint. Nonetheless, there was a possible benefit on fibrous tissue as measured by serum markers of collagen turnover, which decreased, and diastolic function improved (E/E' , $p = 0.01$). Whether these favorable effects will translate into morbidity and mortality benefit in a larger trial remains to be determined.

Trials in progress.

TOPCAT is designed to evaluate the effect of spironolactone on morbidity, mortality, and quality of life in patients with HFpEF.^[147] The Aldo-DHF trial will test whether aldosterone receptor blockade by spironolactone 25 mg daily will improve exercise capacity and diastolic function in patients with DHF. Inclusion criteria are age 50 years or older, NYHA type II or III, preserved LV ejection fraction ($\geq 50\%$), and echocardiographic diastolic dysfunction.^[168] The two primary endpoints are changes in exercise capacity (peak VO_2 , spiroergometry) and in diastolic function (E/\dot{e} , echocardiography) after 12 months.

Further trials are in progress to assess the effect of angiotensin receptor inhibition by the angiotensin receptor blocker, neprilysin, combine with valsartan on HF with preserved ejection fraction,^[168A] and on hypertension already treated by valsartan.^[168B]

Overall interpretation.

While awaiting outcome trials, our view is that persisting clinical heart failure, whatever the ejection fraction, requires added therapy by appropriately increased diuretics, renin-angiotensin inhibition, or β -blockade, and that BP reduction may play a role. Vasodilators may also benefit by afterload reduction.^[169]

Right ventricular failure

"For a long time, the importance of right ventricle . . . function has been neglected."^[170] Right ventricular (RV) physiology is characterized by its close relationship with the pulmonary circuit. The right ventricle can accommodate significant changes in preload, but is highly sensitive to increases in afterload. Progressive dilatation and dysfunction can initiate a cycle of oxygen supply-demand mismatch that ultimately leads to RV failure. Echocardiography and cardiac MRI are the primary modalities used for noninvasive assessment of RV function.^[171] The management of RV failure centers on the optimization of preload, afterload, and contractility. Few targeted therapies exist, although novel agents have shown promise in early studies.

LV dysfunction predisposes to RV dysfunction, as after anterior MI.^[170] The right ventricle is the most anterior cardiac chamber, has a triangular shape, and its free wall is thinner than the left ventricle because the right ventricle contracts in a low-impedance system. Importantly, the shape, location, and contraction conditions make the RV chamber assessment by echo technically challenging. RV dysfunction can now be assessed by RV fractional area change of 35% or less.

RV afterload represents the load that the right ventricle has to overcome during ejection. Compared with the left ventricle, the right ventricle demonstrates a heightened sensitivity to afterload change (see Fig. 6-12). Although in clinical practice, pulmonary vascular resistance (PVR) is the most commonly used index of afterload, PVR may not reflect the complex nature of ventricular afterload.

The evidence that guides the management of isolated RV failure is not nearly as well established as the evidence that guides the management of chronic heart failure resulting from LV systolic dysfunction.^[172] Most recommendations are based on either retrospective or small randomized studies.^[173] However, RV failure usually is a component of LV failure except when pulmonary arterial hypertension (PAH) is the underlying cause. Because of ventricular interdependence, RV dysfunction in turn worsens LV dysfunction.^[172] Experimentally, high doses of bisoprolol (10 mg/kg) and carvedilol (15 mg/kg) given to rats have delayed the progression from PH to RV failure^[174] or improved RV function.^[175] Clinically, even after PAH-targeted therapy, RV function can deteriorate despite a reduction in PVR. Such loss of RV function is associated with a poor outcome, irrespective of any changes in PVR.^[176]

Specific treatment goals.

Specific treatment goals^[173] include optimization of preload, afterload, and contractility. The use of β -blockers, standard in LV failure, has not been well explored in RV failure. Maintenance of sinus rhythm and AV synchrony is especially important in RV failure because atrial fibrillation and high-grade AV block may have profound hemodynamic consequences. Ventricular interdependence also is an important concept to consider when tailoring therapy. Excessive volume loading may increase pericardial constraint and decrease LV preload and cardiac output through the mechanism of ventricular interdependence. Alternatively, hypovolemia may decrease RV preload and cardiac output. In acute RV failure, every effort should be made to avoid hypotension, which may lead to a vicious cycle of RV ischemia and further hypotension.

Pulmonary hypertension

Secondary pulmonary hypertension.

Although guidelines contain detailed recommendations regarding PAH, they contain only a relatively short paragraph on the other, much more frequent forms of PH, including PH secondary to left heart disease (Fig. 6-13). PH is present in 68% to 78% of patients with chronic severe LV systolic dysfunction and is commonly associated with RV dysfunction.^[177] In contrast, PAH focuses on a relatively small subset of all patients with PH, a condition that most commonly occurs secondary to pulmonary venous hypertension in patients with CHF.

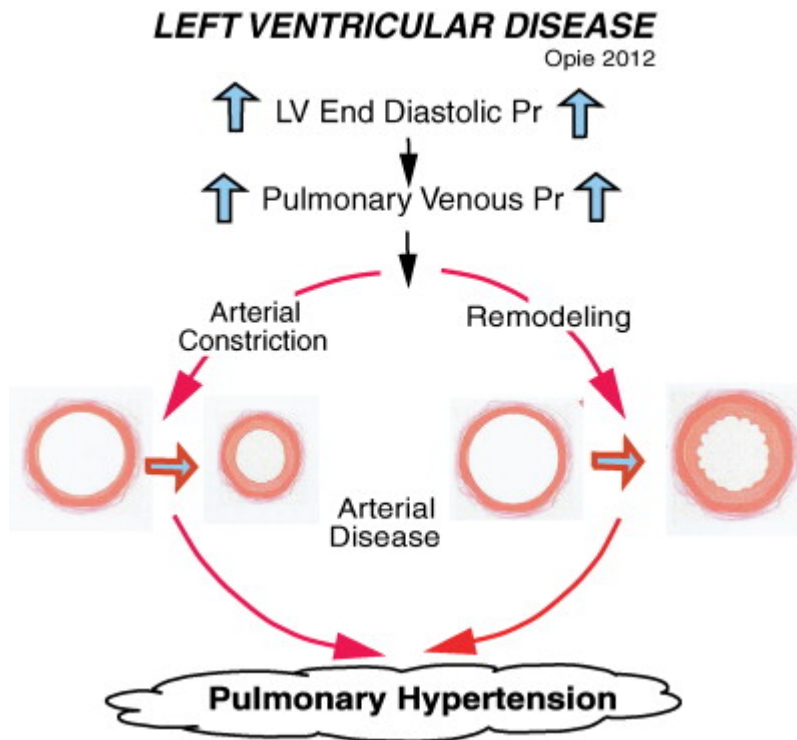


Figure 6-13 How left ventricular (LV) disease can evolve into secondary pulmonary hypertension. First, the LV end-diastolic pressure (Pr) increases, leading to an indirect increase in the pulmonary venous pressure. Arterial constriction and remodeling both predispose to pulmonary arterial hypertension. (Figure © L.H. Opie, 2012.)

Measurement of pulmonary artery pressure.

The prevalence of PH in chronic heart failure is highly dependent on patient selection and the threshold of pulmonary artery (PA) systolic pressure used. PA pressure can be measured invasively by right heart catheterization (gold standard) or noninvasively by Doppler echocardiography. Using the definition of a RV pressure gradient of more than 35 mm Hg (equivalent to an estimated PA systolic pressure >45 mm Hg), 7% of 1380 patients with HF had PH.^[178] In that situation, prime therapy is that of LV failure. But what is specific therapy for PAH? The presence of PAH remains an important independent predictor of mortality, despite powerful associations with other well-established markers of poor outcome such as mitral regurgitation, plasma markers, or elevated LV filling pressure such as NT-proBNP, as well as LV and RV dysfunction.

Drugs currently used to treat patients with PAH (prostanoids, ET receptor antagonists, and PDE-5 inhibitors) have not been well investigated in PH secondary to LV disease (Fig. 6-14).^[179] Clearly more studies are needed in this common situation. However, despite such lack of evidence-based efficacy data, a current trend is toward the use of targeted PAH drugs in patients with PH associated with left heart disease. This trend is supported by a small study showing that sildenafil lowered PVR and improved exercise capacity

and quality of life in patients with heart failure complicated by PH.^[177] These patients also had prior therapy by diuretics and β -blockers (100%), ACE inhibitor or ARB (77%), spironolactone (76%), digoxin (65%), and an implantable cardiac defibrillator (83%). Mechanistically, short-term cyclic GMP-enhancing treatment with sildenafil and BNP infusions improved LV diastolic distensibility in vivo, in part by phosphorylating titin.^[180] The proposal is that these agents might act directly on cardiac proteins in addition to vasodilating.

PULMONARY ARTERIAL HYPERTENSION

Opie 2012

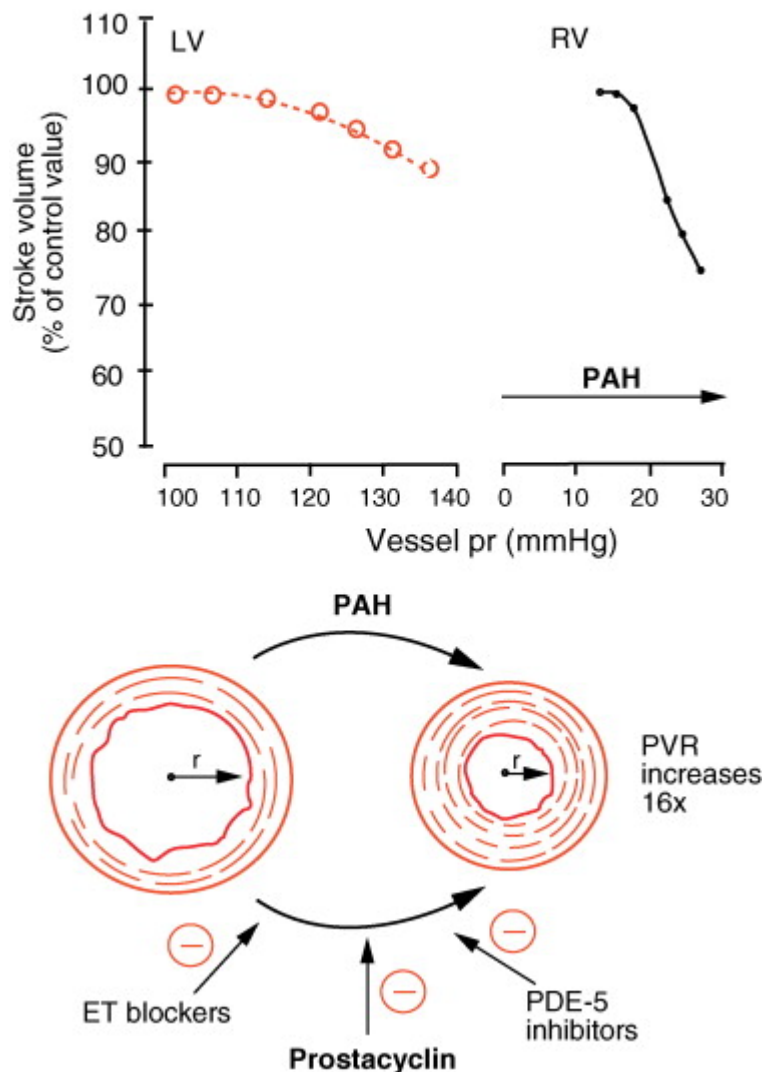


Figure 6-14 Increased intraarterial pressure in pulmonary arterial hypertension (PAH) leads to a much sharper fall in stroke volume than does increased left ventricular (LV) pressure (*upper panel*). To decrease the intraarterial pressure in PAH, the major vasodilator drugs are endothelin (ET) blockers and prostacyclin and phosphodiesterase (PDE)-5 inhibitors (*bottom panel*). PVR, pulmonary vascular resistance; RV, right ventricle. (Figure © L.H. Opie, 2012.)

Pulmonary arterial hypertension

PAH is a rare and incurable progressive disease, including idiopathic PAH, heritable PAH, and PAH secondary to other diseases. Idiopathic PAH is panvasculopathy in which clones of endothelial cells proliferate and give rise to plexiform lesions, the pathologic hallmark of this condition, thereby promoting complex vascular lesions with near-total or total lumen obliteration^{[181],[182]} acting by multiple mechanisms including increased serotonin release. Thus there is increasing vascular smooth muscle damage.^[182] The

functional consequences include decreased endothelial NO production and increased PDE-5 expression and activity in both PA and in the RV muscle cells. The overall result is an increase in PVR in a disease that affects both the PA and the right ventricle.

These obstructive proliferative changes in the lung microcirculation promote RV hypertrophy, eventually leading to right heart failure and premature death. PAH can occur in isolation (primary pulmonary hypertension), or be related to other diseases such as human immunodeficiency virus (HIV) infection, congenital heart disease, connective tissue disorders like scleroderma^[183] and systemic lupus erythematosus, or idiopathic pulmonary fibrosis. PAH can also be induced by substance abuse with appetite suppressants, cocaine, or other drugs. Optimal therapy remains undecided.^[184]

Catheter diagnosis.

Heart catheterization is required to diagnose PAH: a mean PA pressure of 25 mm Hg or more and a PVR greater than 3 Wood units.^[181] As this is a pulmonary vascular disease, the diagnosis also requires exclusion of underlying LV dysfunction (PCWP less than 15 mm Hg). Further exclusions are thromboembolism and parenchymal lung disease.^[181]

In PAH, the RV adaptation to chronic pressure overload is related not only to the levels of vascular resistance (steady afterload), but also to PA stiffness (pulsatile load). Indexes of PA stiffness (elasticity, distensibility, capacitance, stiffness index beta, and pulse pressure) were independently associated with the degree of RV dysfunction, dilation, and hypertrophy in PH. Such increased PA stiffness is associated with reduced survival in PH.^[185]

Therapeutic options.

There is no cure for PAH, but treatment options include prostanoids, PDE-5 inhibitors, and ET-receptor antagonists. A metaanalysis including all therapy types in 21 trials on 3140 patients found a reduction in all-cause mortality of 43% (RR 0.57; CI 0.35-0.92; P = 0.023).^[186] Vasodilators as a group give a 39% mortality reduction.^[184]

Prostacyclins.

Epoprostenol (Flolan) is the only PAH-specific therapy with demonstrated survival benefit in a randomized, prospective clinical trial.^[187] Although continuous infusions of intravenous epoprostenol or subcutaneous treprostinil give benefit, both are limited by the need for meticulous catheter care, continuous infusion, and daily preparation.

Phosphodiesterase-5 inhibitors.

PDE-5 inhibitors vasodilate by acting on PDE-5 in the pulmonary and systemic vasculature. Furthermore, vascular remodeling can be promoted by decreased proliferation and increased apoptosis of PA smooth muscle cells.^[181] RV inotropy also increases.^[181] There is also a direct action on the lungs, in which expression of PDE-5 is suppressed. Thus sildenafil also preferentially improves blood flow to well-ventilated regions of the lung in patients with lung disease such as idiopathic pulmonary fibrosis, another cause of PAH, with symptomatic benefit.^[188] The PDE-5 inhibitors sildenafil (Revatio) and tadalafil (Adcirca) are FDA approved for the treatment of PAH, with sildenafil also approved by the European Medicines Agency. Mortality trials are not available.

Endothelin receptor antagonists.

The first oral therapy approved for therapy of PAH was bosentan.^[189] Bosentan gives combined ET_A/ET_B receptor antagonism. Selective ET_A antagonists (sitaxsentan approved in Europe; ambrisentan approved in the United States) theoretically preserve the vasodilatory action of the ET_B receptor. However, no trial data show whether selective ET_A antagonism is better than combined ET_A and ET_B antagonism (also see macitentan, next section). Furthermore, there are no robust trial data to indicate improved survival with any of these agents.^[182]

Macitentan is a dual ET_A/ET_B receptor antagonist with high lipophilic affinity with inhibitory constants in nanomolar range.^[190] Experimentally, it improves survival in monocrotaline-induced pulmonary hypertensive rats and protects against end-organ damage in diabetes. ET-1 can change tissue structure and induce

fibrosis. Tissue ET-1 acts via binding to the two G protein-coupled receptors (ET_A/ET_B) located on a large variety of cell types such as endothelial cells and macrophages. Blockage of both is required to oppose the overall pathologic effects of ET-1 stimulation.

Seraphin study.

On April 30, 2012, Actelion (SIX: ATLN) announced the initial analysis of the event-driven study SERAPHIN with macitentan in 742 patients with PAH and treated for up to 3.5 years.^[191] Macitentan decreased the risk of a morbidity-mortality event during the treatment period versus placebo by 45% in the 10 mg–dose group ($p < 0.0001$) and 30% ($p = 0.01$) in the 3-mg group.

Combination therapy.

In patients with primary PAH the addition of sildenafil to long-term intravenous epoprostenol therapy improved exercise capacity, time to clinical worsening, hemodynamic measurements, and quality of life.^[192] Conversely, the addition of epoprostenol to sildenafil after 2 years of sildenafil treatment did not improve a group of Japanese patients.^[193]

Therapies in evolution.

The evolution of therapies is very active. Listed alphabetically, the major drugs in development are as follows. *Cicletanine* counters endothelial dysfunction in PAH by coupling to endothelial nitric oxide synthase.^[194] *Fasudil* is an Rho-kinase inhibitor that counters calcium sensitization and vasoconstriction. Experimentally, PAH was more improved by fasudil than by bosentan or sildenafil, whereas combining bosentan or sildenafil with fasudil had no synergistic effect.^[195] *Imatinib* is an inhibitor of the activity of the vasculopathic protease-activated receptor–2 found on mast cells and platelets (see Fig. 9-3) and increased in PAH.^[196] *Riociguat* activates soluble guanylate cyclase that in turn improves endothelial function and lessens fibrous tissue remodelling.^[197] *Selexipag* is a direct and highly prostaglandin receptor agonist that significantly decreased PVR in a phase 2 study.^[198] *Terguride*, a dopamine agonist with antiserotonergic and antifibrotic properties,^[199] is entering clinical studies.

Pulmonary arterial hypertension in scleroderma.

PAH in scleroderma (progressive systemic sclerosis) is an example of PAH secondary to connective tissue diseases. Survival depends on severity of RV dysfunction, the degree of renal impairment, and the cardiac adaptation to pulmonary vascular disease.^[200] The PAH is triggered by circulating autoantibodies that damage the endothelium and activate fibroblasts. Approved therapies include prostacyclins, ET antagonists, and PDE-5 inhibitors. *Prostacyclins* (continuous infusions of intravenous epoprostenol or subcutaneous treprostinil) give benefit but are limited by the need for meticulous catheter care, continuous infusion, and daily preparation. *Selective ET receptor A antagonists* (sitaxsentan approved in Europe; ambrisentan approved in the United States; bosentan) preserve the vasodilatory action of the ET B receptor. The *PDE-5 inhibitors* sildenafil (three times daily) and tadalafil (once daily) are approved for use in PAH (including PAH-systemic sclerosis) in the United States. However, the response to all such therapies is limited.^[183]

Drug-induced pulmonary arterial hypertension.

There are many drugs that have been linked to PAH. Among the best-known are Fen-Phen, fenfluramine, and fenfluramine derivatives, which are associated with PAH, heart valve disease, and cardiac fibrosis. Fenfluramine was withdrawn from the US market in 1997 but lingered on in Europe. It induces gene dysregulation in human PA smooth muscle and endothelial cells.^[201] HIV infection and treatment with highly active antiretroviral therapy including HIV protease inhibitor ritonavir (RTV) may be associated with endothelial dysfunction and PAH. Dasatinib (Sprycel) is an anticancer drug that can induce severe precapillary PAH when given for certain acute and chronic leukemias.^[202] In a large French Registry of approximately 3000 patients, there were 64 reports of PAH.^[202] The FDA warned in October 2011 that symptoms of heart failure might arise any time after initiation of therapy, even after 1 year. Thereupon the drug should be stopped, and if required, diagnostic right heart catheterization undertaken.

Heart failure in women

Menopause influences the pattern of disease, with the incidence of coronary heart disease increasing

thereafter. Nonetheless, women have a lower baseline risk for CHD at all ages except perhaps beyond 80 years. Thus it is not a simple issue of being pre- or postmenopausal.

Patterns of heart failure are different. Women are relatively neglected in clinical trials, although the DIG study warned of increased mortality of unknown cause in women with heart failure compared with men (Table 6-8). Women are more likely to have HFpEF with a better prognosis than men. On the other hand, in HFrEF, women are older with a lower quality life, and more often with concomitant diabetes. Device therapy is underused.

Table 6-8 -- Gender and Cardiovascular Differences

Estrogen vascular effects: Favorable lipid profile, lower LDL, higher HDL; facilitates NO-vasodilation; antifibrotic.
Pregnancy may precipitate or worsen HF; physiologic 30%-50% increase in CO. Peripartum cardiomyopathy*: defined as deterioration in cardiac function between the last month of pregnancy and up to 5 months postpartum with no other cause evident.
Therapy for HF in pregnancy: ACE inhibitors, ARBs and spironolactone-eplerenone contraindicated in all trimesters (this C/I is not mentioned by Shin et al.).
Menopause: Risk of HF rises, estrogen deprivation.
Failure of HRT to give CV protection in prospective trials.
HRT in HF may vasodilate and block inflammatory cytokines, but no prospective trials.
Patterns of HF: Women more likely to have HFpEF; better prognosis than in men. In HF with reduced EF, women older, lower QOL, diabetes more often associated.
HF management: Women underrepresented in all trials, also in Dig trial (22%).
Digoxin for HF: ^[140] ↑ risk of all-cause death in women (HR, 1.23). ? Interaction with HRT.
Device therapy: Underused, women have more LBBB, a criterion for CRT.

Based on review data in Shin JJ, et al. *Heart failure in women. Clin Cardiol* 2012; 35:172–177.

ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; C/I, confidence interval; CO, cardiac output; CRT, cardiac resynchronization therapy; CV, cardiovascular; EF, ejection fraction; HDL, high-density lipoprotein; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; HRT, hormone replacement therapy; LBBB, left bundle branch block; LDL, low-density lipoprotein; NO, nitric oxide; QOL, quality of life.

* See section on page 216.

Management of heart failure and treatment of cardiomyopathies in pregnant women and postpartum requires special consideration (Table 6-8). During pregnancy, ACE inhibitors, ARBs, spironolactone, eplerenone, and renin inhibitors are contraindicated because of fetotoxicity. Therefore such medication ideally needs be terminated and replaced. Nonetheless, there are isolated reports that eplerenone is less antiandrogenic than spironolactone when used in pregnancy for primary aldosteronism without the expected potent antiandrogenic effects that can cause ambiguous genitalia in a male fetus.^[203] Diuretics should be used sparingly as they may decrease blood flow to the placenta and have an effect on lactation.^[204]

Peripartum cardiomyopathy

PPCM is a not-so-rare (up to 1:1000) yet serious type of idiopathic heart failure without any underlying determinable heart disease during the last month of pregnancy or the first 5 months postpartum. The incidence varies worldwide but is high in developing nations; the cause of the disease might be a combination of environmental and genetic factors.^[205] In Turkey, of 42 consecutive women with PPCM only 47.6% had a full recovery, with an average time to complete recovery of 19.3 months after initial diagnosis.^[206] The cause of PPCM is uncertain but one proposal is that mutations associated with familial dilated-cardiomyopathy genes overlap with those found in PPCM, thus suggesting a clinical overlap of these two diseases. More specifically, proinflammatory factors and autoimmune processes may play a role.^[207] There is increasing evidence that the disease occurs as a result of the consequences of imbalanced

oxidative stress leading to proteolytic cleavage of prolactin into a potent angiostatic factor with inhibition of cardioprotective STAT-3.^[208] This study suggested that inhibition of prolactin release could be a novel therapeutic strategy for PPCM.

Peripartum cardiomyopathy–targeted therapies.

Intravenous immunoglobulin, pentoxifylline, and bromocriptine have all been used in small trials.^[205] These all need further extended controlled studies. *Immunoglobulin* is most logical if given for patients with proven myocarditis. In a small retrospective study, women treated with immune globulin had a greater improvement in ejection fraction during early follow-up than patients treated conventionally.^[209] *Pentoxifylline* 400 mg three times daily, added to prior conventional therapy in 30 patients was the only independent predictor of outcome ($P = 0.04$).^[210] However, the control and pentoxifylline groups were studied sequentially. *Bromocriptine* is a dopamine-2D agonist that inhibits prolactin release and thus specifically acts on the disease molecular mechanism. A recent small prospective randomized pilot study showed that bromocriptine added to standard heart failure therapy had beneficial effects on ventricular ejection fraction and clinical outcome in patients with acute severe PPCM.^{[204],[211]} Bromocriptine was given as 2.5 mg twice daily for 2 weeks followed by 2.5 mg daily for 6 weeks.

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Summary

- 1. Heart failure is a complex, potentially fatal condition.** It includes acute heart failure, often needing therapy by intravenous diuretics, vasodilators and possibly inotropes; and chronic heart failure, which may present as classic systolic failure that requires neurohumoral antagonism by ACE inhibitors (or ARBs), β -blockers, and aldosterone blockers, besides diuretics. Equally frequently, heart failure may present with a preserved ejection fraction and diastolic dysfunction, and with less clear therapeutic options.
- 2. Acute heart failure with pulmonary edema.** Acute heart failure with pulmonary edema is not a uniform entity. The problem is the many different causes and varying clinical presentations. Intravenous furosemide remains fundamental, yet the dose should be limited. New agents acting on specific mechanisms are a promising approach.
- 3. Cardiogenic shock with or without pulmonary edema.** β -receptor stimulatory inotropes are often used in the acute therapy of severe heart failure, but these drugs may further damage the myocardium. The problem of β -receptor downregulation may require added PDE inhibition. Available drugs include dobutamine and dopamine. Vasopressin helps in septic or perianesthetic shock. Epinephrine gave similar outcomes to norepinephrine plus dobutamine in septic shock.
- 4. Inotropic-dilators (PDE inhibitors).** Intravenous preparations with their inotropic and vasodilator effects should be especially useful in patients with β -receptor downgrading, as in acute-on-chronic severe CHF or during prolonged therapy with dobutamine or other β_1 -stimulants, or after chronic β -blockade. Thus milrinone has a limited place in the management of short-term therapy of heart failure.
- 5. Load reduction and vasodilators.** These are often chosen in severe acute heart failure, especially when the BP is relatively well maintained, to relieve the burden on the failing myocardium. Such agents include furosemide, nitrates, and nitroprusside. They may be carefully combined with agents that give inotropic or pressure support such as dobutamine or dopamine.
- 6. Five current approaches to chronic heart failure.** The five major approaches to the management of CHF are, first, elimination and prevention of fluid retention; second, the use of ACE inhibitors as standard therapy; third, inhibition of the β -adrenergic response by β -blockers initially given in low doses but up-titrated to maximally tolerated doses; fourth, inhibition of aldosterone effects by spironolactone and eplerenone; and, fifth, the use of ARBs. The combination of nitrates and hydralazine is also a useful adjunct in select patients, including self-identified blacks. In addition, metabolic modulators, if available, may give added benefit. The “vaptans” are registered for use in symptomatic heart failure resistant to fluid restriction. Gene therapy is not yet available. General measures include intense disease-management programs, exercise training, and correction of anemia. Mechanical and electrical devices (ICDs, CRT, and mechanical assist devices) are increasingly used with substantial trial support.
- 7. Digoxin reappraised.** In the past, digoxin was standard therapy in CHF, at a time when inotropic therapy was regarded as desirable. Digoxin use in patients already optimally treated by a combination of mortality-reducing drugs such as β -blockers, ACE inhibitors and ARBs, and aldosterone blockers has never been tested. A small unproven mortality benefit may exist at blood levels less than 1 ng/mL, converting to a substantially increased mortality at higher blood levels. Inexplicably, women in the large DIG study had an increased mortality whereas men did not. In view of many uncertainties and without clear outcome trials in the current era, and in the light of new therapies, we do not recommend digoxin for heart failure. In ambulatory patients already receiving digoxin, the best prognosis is with low blood levels (low-dose digoxin \leq 0.125 mg/day).
- 8. Preserved systolic function.** Preserved systolic function despite clinical heart failure is a common and serious condition echocardiographically, and is the result of *DHF*. This condition is relatively more common in women. In one large trial, adding the ARB candesartan to prior therapy reduced the secondary endpoint (cardiovascular death or hospitalization for CHF, MI, or stroke). However, only

19% were receiving prior ACE inhibition. Renin-angiotensin inhibition should be considered for all patients with heart failure, whatever the ejection fraction. In general, the major benefit of drug treatment of heart failure with preserved systolic function is improved exercise tolerance, a major positive for the patient, yet without mortality decrease in a metaanalysis.

9. **PAH.** The presence of PAH secondary to chronic left heart failure is an important independent predictor of mortality. Therapy is not well defined but may include sildenafil and related compounds. Primary PAH is much rarer yet much better studied. It may occur secondary to various pulmonary vascular diseases, including scleroderma (systemic sclerosis), or as an idiopathic event. In the latter case, therapy is well defined and includes prostanoids, PDE-5 inhibitors, and ET blockers. New agents are in development. Nonetheless, the prognosis remains grave.
10. **Pregnancy.** During pregnancy ACE inhibitors, ARBs, spironolactone, eplerenone, and renin inhibitors are contraindicated because of fetotoxicity. Diuretics should be used sparingly as they may decrease blood flow to the placenta and have an effect on lactation. Molecular therapy in the form of bromocriptine may be specific therapy for peripartum cardiomyopathy.
11. **Women and heart disease.** The influence of menopause and of aging in women is under increasing study. There appear to be lifelong biological differences in cardiovascular disease patterns. There are still deficiencies in knowledge of the ideal therapy of heart failure in women.
12. **The future therapy of heart failure.** It is dangerous to be a prophet. Advances are emerging. New drugs are based on new mechanisms. Ultimately heart failure is a biological problem and the solution will lie in the prevention of the causes of the disorder and in the ability to replace or repair the myocardial cells using gene therapy or stem cell regeneration.

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