Congestive heart failure is a common clinical syndrome, with a relatively poor prognosis in its advanced stages. During the development of heart failure, there is a decline in myocardial contractility and activation of neurohormonal systems. An overshoot of some of these compensatory mechanisms sets the stage for therapeutic interventions. Any of the three therapeutic classes of drugs (inotropic drugs, diuretics or vasodilators) can be used as first-line therapy. Other classes can be added to produce additive effects on ventricular function. Because vasodilators have been shown to prolong life, they should be used routinely in patients with heart failure. Arrhythmias and sudden death are relatively common in heart failure, although the value of antiarrhythmic therapy is less certain. Although current therapy is very helpful in patients with heart failure, it is clear that preventive approaches will be more effective in decreasing morbidity and mortality.

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Congestive heart failure is a common clinical syndrome and, in its advanced stages, has a grave prognosis. Much has been learned about this syndrome, especially through a better understanding of its pathophysiology. The purpose of this review is to update our knowledge of congestive heart failure, and especially relate our current therapy to an understanding of its pathophysiology.

Epidemiology (1)

It is estimated that about 3 million Americans have congestive heart failure. This represents about 1% of the population. For those aged >75 years, the prevalence of congestive heart failure is about 10%. Congestive heart failure is now the most common hospital discharge diagnosis for those over the age of 65. Approximately 400,000 individuals develop heart failure each year.

Age dependence of congestive heart failure (Fig. 1). As expected, there is a significant increase in the incidence of congestive heart failure at advanced ages (2). This seems to correspond somewhat with the increase in left ventricular hypertrophy seen with age, as determined by echocardiography (3).

Mortality (Fig. 2). The mortality from congestive heart failure has been detailed in several studies. It appears that women have a lesser mortality after the diagnosis of congestive heart failure than do men. The 5 year mortality in men is about 60%, whereas in women it is about 45%. When symptoms of heart failure occur at rest (New York Heart Association functional class IV), however, the 1 year mortality rate approaches 50% (4). About 40% of the time, the mode of death is sudden, implicating serious arrhythmias as the underlying cause (5).

Although the mortality from cardiovascular disease has been steadily declining since 1968 (6), the incidence and
prevalence of congestive heart failure have been increasing. These trends may be due, in part, to the aging population, and in part to the improvements in therapy that have allowed patients with cardiovascular disease to live longer, so that congestive heart failure becomes a more common clinical problem.

**Definition**

A traditional definition of congestive heart failure is “the inability of the heart to deliver enough blood to peripheral tissues to meet metabolic demands.” This definition, however, does not fully describe the syndrome of congestive heart failure as we see it in clinical practice. The two major symptom complexes of congestive heart failure are dyspnea (particularly dyspnea with exercise) and fatigue. It is presumed that these two major symptoms relate to the two major hemodynamic abnormalities of congestive heart failure—namely, an increase in left atrial pressure and a decrease in cardiac output. Thus, from a functional viewpoint, it is clear that congestive heart failure also includes the symptoms of dyspnea and fatigue and a decrease in exercise tolerance. Therefore, there is not only a decrease in peripheral blood flow to meet metabolic demands, but also an increase in atrial pressures leading to the signs and symptoms of either right or left heart failure, or both.

**Etiology**

In the Framingham study (7), which prospectively examined the development of heart failure in a cohort of the population of Framingham, Massachusetts, it appeared that hypertension was one of the major factors leading to heart failure. Over the past 2 decades, however, better recognition and treatment of high blood pressure have reduced the relative importance of this factor. Certainly, better treatment of hypertension has dramatically reduced the incidence of stroke. In current series in the United States, it appears that in about 50 to 75% of patients with heart failure, coronary artery disease is the underlying cause (8). Hypertension may be a contributing factor in some patients, but is clearly less important than myocardial infarction and ischemia. The next most common cause appears to be cardiomyopathy. Rheumatic heart disease is declining significantly in the United States, although valvular heart disease due to mitral regurgitation or aortic stenosis is still reasonably common in the population at large. Congenital heart disease represents only a small portion of patients presenting with congestive heart failure.

**General Principles**

When a patient presents with the signs and symptoms of congestive heart failure it is important that the etiology of this syndrome be carefully identified. In addition to history and physical examination, echocardiography and other non-invasive and invasive tests can be very helpful in assessing the precise cause of the congestive heart failure. It is also important to determine whether the signs and symptoms are due primarily to ventricular systolic dysfunction, diastolic dysfunction or a combination of the two. In most cases systolic dysfunction, as manifested by a decreased ejection fraction, will be the most common cause of congestive heart failure. In a minority of cases, diastolic dysfunction will be the predominant cause (9). The latter circumstances would include patients with hypertrophic cardiomyopathy, hypertrophy from any cause, restrictive cardiomyopathy, pericardial disease, certain infiltrative diseases such as amyloid or any process that impedes filling of the ventricle and thus leads to an increase in atrial pressures when cardiac output is increased. It is likely that almost all patients who have systolic dysfunction have some element of diastolic dysfunction as a contributing cause. Our inability to effectively treat diastolic dysfunction, however, limits our ability to provide major therapeutic benefit to patients with this disorder. Certainly if patients have constrictive pericarditis, removal...
of the pericardium can be quite dramatic in improving function. Similarly, valvotomy in patients with mitral stenosis can also produce a dramatic benefit in what is primarily a filling problem of the left ventricle. Some patients with severe hypertrophic cardiomyopathy may benefit from calcium channel blocker therapy, which can increase left ventricular volume at the same end-diastolic pressure (10). Similarly, in patients with severe hypertensive hypertrophy, which may restrict ventricular filling, control of hypertension with antiadrenergic drugs, the angiotensin-converting enzyme inhibitors or calcium channel blockers can cause regression of the hypertrophy (11) and thus reduce diastolic dysfunction. It is clear, however, that we need to learn much more about diastolic dysfunction and ways to alter it to effectively treat this component of congestive heart failure.

Our current understanding of congestive heart failure is based on our understanding of changes that occur in the myocardium as well as peripheral changes, including neurohumoral alterations, that affect the circulation. These changes will be described in the next sections.

**Decrease in Myocardial Contractility**

A fundamental problem for patients with systolic dysfunction is a decline in myocardial contractility. This can be the result of prolonged pressure or volume overload or an intrinsic decline associated with cardiomyopathy. In patients with ischemic heart disease, loss of muscle with myocardial infarction imposes an additional volume and wall stress overload on the remaining normal myocardium. These changes lead to remodeling of the ventricle over time and, eventually, to a similar intrinsic decline in contractility. In general, therefore, therapy has been directed toward earlier recognition and treatment of increased loading conditions of the ventricle. For example, angiotensin-converting enzyme inhibitors may prevent remodeling and delay or attenuate the irreversible decline in contractility that occurs with increased loading after myocardial infarction (12).

**Indexes of reduced muscle contraction.** A reduction in myocardial contractility is manifested by decreased force development, decreased rate of force development and decreased velocity of shortening at given loading conditions. These changes are frequently accompanied by a delay in relaxation (Table 1). These indexes of muscle contraction (13) are reflected in the intact heart by a decrease in ejection fraction and stroke volume and by a shift downward in the ventricular function curve with an increase in atrial pressure.

**Biochemical changes.** A number of biochemical changes have been noted to accompany the process of congestive heart failure. Although it is outside the scope of this review to examine all of these, a few are listed in Table 1. A reduction in contractility is frequently accompanied by a shift in myosin isozymes, such that rapidly contracting V1 forms with high adenosine triphosphatase (ATPase) activity are converted into slower contracting V4 forms with slower ATPase activity (14). The relation between maximal velocity of shortening and myosin ATPase activity seen over a wide variety of species (15) also occurs in animal models of congestive heart failure and in patients. A reduction in velocity of shortening and actomyosin ATPase activity has the potential benefit of reducing oxygen consumption and thus conserving energy in circumstances where it may be limited. Clearly, however, this compensatory aspect does not make up for the dramatic reduction in function that leads to reduced cardiovascular performance.

Hypertrophy is one of the most important compensatory mechanisms available to heart muscle as function decreases, and it is accompanied by an increase in connective tissue that may stiffen the diastolic properties of the heart (16). In animal models of heart failure, calcium overload may play an important role in the development of congestive heart failure (17). This may occur through damage of the sarcolemma or perhaps through increased calcium entry due to increased sympathetic tone or increased sodium-calcium exchange. Certainly, the sarcoplasmic reticulum exhibits decreased function (18). An excess of myoplasmic calcium can reduce mitochondrial function and decrease the production of high energy phosphates. At least in animal models of congestive heart failure, such as the hereditary cardiomyopathy of the Syrian hamster, calcium overload plays a major role (19). The calcium channel blocker, verapamil, is effective in attenuating or treating this form of experimental heart failure. Microvascular spasm (20) has also been implicated in some experimental models of congestive heart failure and has responded to a vasodilator, such as prazosin (21). It is not clear, however, whether these specific biochemical changes in experimental models of heart failure have any application to the clinical syndrome of congestive heart failure.

**Sympathetic nervous system and neuroendocrine activity.** The activity of the sympathetic nervous system is increased in congestive heart failure (22). A reflex increase in sympathetic tone is presumably designed to maintain cardiovascu-
lar compensation by increasing heart rate and contractility. This increased tone leads to a decline in stores of norepinephrine in the myocardium (23) that spill over into the circulation. In some animal species there is also a decline in the production of norepinephrine (24). Increased catecholamines lead to a decline in beta-2-receptors (25), although beta-2-receptors may be little affected. These latter changes reduce the responsiveness of the myocardium to catecholamines, but the marked increase in plasma catecholamines in congestive heart failure is still sufficient to produce important sympathetic support of the circulation. Some studies in dilated cardiomyopathy suggest that this increased sympathetic drive may actually be deleterious. Some patients with dilated cardiomyopathy have responded beneficially to low dose metoprolol (26); this finding suggests that excess sympathetic drive may be directly harmful to the heart. Certainly high dose catecholamine infusions can directly cause myocardial necrosis in experimental animals (27). The combination of tachycardia and prolonged sympathetic stimulation may be deleterious in some patients with congestive cardiomyopathy. Tachycardia in and of itself not only increases myocardial oxygen demand, but also, by reducing diastolic time, can reduce coronary blood flow to the myocardium and contribute to an imbalance between supply and demand.

Although beta-blocker therapy may be beneficial for some patients with cardiomyopathy, it is clear that it does not have widespread application to all forms of heart failure. In fact, beta-blockade can suddenly and dramatically worsen function in some patients who have severe congestive heart failure. The precise role, therefore, of the sympathetic nervous system and its potential benefit and harm have yet to be firmly elucidated in different patient subsets.

**Pressure and volume overloading.** If increased loading factors are deleterious to heart muscle, it is clear that unloading therapy may be one of the most beneficial ways to attenuate the adverse effects of prolonged pressure or volume overloading. In general, the decline in contractility that accompanies severe heart failure appears to be mostly irreversible and to continue in a downward spiral. Relief of pressure or volume overload in circumstances of valvular disease, however, has shown that there can be some restitution of function (28). This emphasizes the importance of earlier intervention before these irreversible changes produced by pressure and volume overloading cause an irreversible decline in cardiac contractility.

### Neurohormonal and Other Peripheral Factors in Congestive Heart Failure

**Increased sympathetic nerve reflexes and plasma catecholamines.** A number of neurohormonal factors contribute to the syndrome of congestive heart failure. Three hormonal systems that are activated in congestive heart failure include the renin-angiotensin-aldosterone system (29), the sympathetic nervous system (22) and arginine vasopressin (antidiuretic hormone) (30). The marked increase in catecholamines is probably a reflection of the overall severity of the heart failure state (31), because it is presumed that this increase in sympathetic tone is intended to be compensatory. For example, the decrease in stroke volume and cardiac output that accompanies heart failure leads to a decrease in arterial pressure. The baroreceptor-mediated reflex increase in systemic vascular resistance produced by an increase in sympathetic tone would initially be helpful in maintaining arterial pressure during a decrease in cardiac output. Similarly, the decline in contractility that occurs in heart failure would be supported by the increased activity of the sympathetic nervous system, which could thus help to maintain stroke volume and cardiac output. Not only is there an increase in plasma catecholamines, but also there is an abnormal response of the sympathetic nervous system to physiologic interventions. Some examples are listed below.

> When patients with heart failure are subjected to upright tilt, there may be no change in plasma norepinephrine, although in normal subjects there would be an increase in plasma norepinephrine levels (32) This blunting of baroreceptor responses appears to form a component of the heart failure syndrome (33). Whether this is due to a smaller reduction in atrial pressures, changes in afferent stimulation or changes in central integration is not clear. Increasing or decreasing arterial pressures also does not produce the same responsiveness in patients with congestive heart failure. During exercise there may be a more abrupt increase in plasma norepinephrine at lower work loads in patients with failure, although the relative change in plasma norepinephrine may be less appropriate to the maximal achievable exercise response (34). Thus, overall there may be some blunting of the catecholamine response to exercise.

**The arginine vasopressin system.** This system is also increased in most patients with congestive heart failure (30). Because this antidiuretic hormone is such a potent vasoconstrictor, it could contribute to the peripheral vasoconstriction which can be so deleterious to patients with severe heart failure. Studies (35) suggest that osmoreceptor function is

### Table 2. Neurohormonal and Peripheral Changes in Congestive Heart Failure

<table>
<thead>
<tr>
<th>Neurohormonal</th>
<th>Peripheral factors</th>
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<tbody>
<tr>
<td>1. Increased plasma catecholamines</td>
<td>1. Increased systemic vascular resistance</td>
</tr>
<tr>
<td>2. Activation of renin-angiotensin-aldosterone system</td>
<td></td>
</tr>
<tr>
<td>3. Increased arginine vasopressin (antidiuretic hormone)</td>
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<tr>
<td>4. Increased atrial natriuretic factors</td>
<td>2. Blunting of baroreceptor reflexes</td>
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<td></td>
<td>3. Decreased vasodilatory response of peripheral vasculature</td>
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<td></td>
<td>4. Altered regional flows</td>
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<td>5. Venoconstriction</td>
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essentially intact in patients with congestive heart failure. In a few patients, arginine vasopressin may directly contribute to adverse sympathetic tone.

**Atrial natriuretic hormones.** Patients with heart failure generally have higher levels of atrial natriuretic factor than do normal persons (36). Data suggest that the effects of atrial natriuretic factor on diuresis are diminished in patients with congestive heart failure. Although infusion of this hormone has produced increases in cardiac output and increased renal excretion (37), it is unclear that this will be a major therapeutic intervention in relation to all of the other drugs available in patients with congestive heart failure.

The renin-angiotensin-aldosterone system. This system is also activated in patients with congestive heart failure (29). The three primary mechanisms whereby renin increase is promoted include reduced serum sodium, an increase in sympathetic tone and decreased blood pressure perfusing the macula densa. All three of these factors are frequently present in patients with congestive heart failure. Furthermore, diuretic usage is extremely common in such patients and may contribute directly to the observed rise in renin activity in this group. Renin, in turn, converts an angiotensinogen made in the liver to angiotensin I, which is an inactive decapeptide. Angiotensin I is then converted to angiotensin II by converting enzyme. Converting enzyme is located everywhere in the body but appears to predominate in pulmonary capillary endothelial cells.

Angiotensin II has three effects that may be deleterious to patients with congestive heart failure. First, it is a potent vasoconstrictor that may contribute to excess systemic vascular resistance. Second, it tends to facilitate sympathetic outflow that may contribute to the already elevated levels of plasma catecholamines. Third, it feeds back on the adrenal gland to release aldosterone and thus further contributes to the increased salt retention seen in patients with heart failure. Patients with a low serum sodium level appear to have the highest renin levels (38). They are also the patients who have the highest mortality rate (39), and may be the most responsive to the angiotensin-converting enzyme inhibitors.

Antagonists to the three neurohormonal systems. The relative importance of the three vasoconstrictor hormone systems was evaluated in a study by Creager et al. (40) (Fig. 3). In that study, patients were given antagonists to the three neurohormonal systems to counteract their vasoconstriction. The resultant hemodynamic response, therefore, represents the ability to reverse the adverse hemodynamic effects of these systems. On average, the antagonist to arginine vasopressin produced only minimal hemodynamic changes. Captopril, which interferes with the renin-angiotensin system, produced moderate beneficial hemodynamic effects, including an increase in cardiac output and a reduction in filling pressures. The greatest changes in hemodynamics were produced by an alpha-adrenergic blocker (phentolamine), which antagonized the peripheral vasoconstrictive effects of increased catecholamines. This produced the greatest change in forward cardiac output and the greatest reduction in filling pressures. These findings suggest that the relative effects of vasoconstriction are produced in order by 1) excess sympathetic stimulation and catecholamines, 2) the renin-angiotensin-aldosterone system, and 3) the arginine vasopressin system.

Peripheral vascular changes: alterations in regional flow. Several peripheral vascular changes accompany the heart failure state. In addition to the increase in systemic vascular resistance, some studies (41) have suggested that there is an inability of the peripheral vasculature to dilate normally in response to stimuli such as hyperemia after transient vascular occlusion. A blunting of the baroreceptor mechanism has also been found and may explain why some vasodilator drugs do not result in an increase in heart rate in the same way that they do in patients with normal ventricular function. A limitation of cardiac output requires that regional flows be preserved for vital organs such as the heart and brain, whereas there may be a substantial reduction of the circulation in the skin, splanchnic bed, skeletal muscle and kidney (42). These alterations in regional flow may contribute greatly to some of the associated signs and symptoms accompanying severe congestive heart failure. In addition to arteriolar vasoconstriction, there is also venoconstriction especially due to increased catecholamines.

**Compensatory Mechanisms**

The four primary determinants of cardiac function are preload, afterload, contractility and heart rate. There is
Deleterious vicious cycles contributing to heart failure. This overshoot in compensatory mechanisms can produce vicious cycles such as those illustrated in Figure 4. The decline in cardiac contractility leads, by potent neurohumoral mechanisms, to an increase in systemic vascular resistance. This increased resistance can act as an increased afterload and impedance to ejection, and thus further reduce cardiac output. The downward spiral continues until a new low steady state level is reached at which cardiac output is lower and systemic resistance higher than is optimal for the circulation. Similarly, a reduction in cardiac output contributes to decreased renal perfusion, which also leads to an increase in salt and water retention. In excess, this can also worsen the heart failure state and contribute to a further downward spiral. It is clear that a complex interaction of a number of factors contributes to the development of heart failure. It is therefore possible for a variety of interventions to counteract the overshoot and thus beneficially affect cardiac function.

Therapeutic Approach to Congestive Heart Failure (Table 3)

After one has identified the syndrome of congestive heart failure, it is mandatory to determine its cause and to assess the relative contribution of diastolic dysfunction. These steps may indicate the need for therapeutic interventions apart from the pharmacologic treatment to be described later. For example, patients with severe aortic stenosis need replacement of the aortic valve. Similarly, patients with other types of valvular disease may be benefited by appro-

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**Table 3. Therapeutic Approach to Congestive Heart Failure**

1. Determine the etiology
2. Evaluate relative importance of diastolic dysfunction
3. Surgical correction where possible
4. Nonpharmacologic treatment
   - A) Reduce salt intake; avoid salt excess
   - B) Reduce physical and emotional stress
5. Pharmacologic approach
   - A) Either diuretic, digoxin or vasodilator as first line therapy
   - B) Add second and third drugs as necessary
   - C) Vasodilators are generally used because they can prolong life
     1) ACE inhibitors
     2) Combination of hydralazine and isosorbide dinitrate
   - D) Add potent inotropic agents if the above is ineffective
     1) Intermediary dobutamine
     2) Phosphodiesterase inhibitors
   - E) For dilated cardiomyopathy consider low dose metoprolol
6. Consider heart transplant for appropriate patients with end-stage heart failure

ACE = angiotensin-converting enzyme.
given intravenously, furosemide directly increases venous capacitance and can acutely reduce left ventricular filling pressure by redistributing blood away from the chest (46). This hemodynamic change is retention of salt and water. This restricts extracellular volume. A number of specific, although rare, circumstances must also be addressed. For example, hyperthyroidism can contribute dramatically to deterioration in patients who have an underlying cause for heart failure. Similarly, anemia and other causes of high cardiac output (44) may contribute to the borderline compensation seen in some patients. When attention has been paid to these nonpharmacologic approaches to therapy, one can then consider the use of drugs from the three major classes of antifailure drugs now available—the diuretics, inotropic agents and vasodilator drugs. These will be discussed in the sections that follow.

**Diuretics**

Under normal circumstances, renal plasma flow is approximately 10% of the cardiac output and thus is about 500 ml/min (45). When mean arterial pressure ranges from about 80 to 200 mm Hg, glomerular filtration rate is kept approximately constant by autoregulation. Below these levels, however, renal blood flow is decreased as arterial pressure is decreased and glomerular filtration may stop at an arterial pressure of about 40 mm Hg. In general, about 20% of the plasma enters the glomerulus is filtered and, as an end result, about 1% of the filtrate is excreted in the urine. In patients with congestive heart failure, there is a reduction in cardiac output and arterial pressure. The renal response to this hemodynamic change is retention of salt and water. This has led to the use of diuretics as the most practical way of improving diuresis. Not only can diuretics be effective in increasing salt and water excretion, but, for example, when given intravenously, furosemide directly increases venous capacitance and can acutely reduce left ventricular filling pressure by redistributing blood away from the chest (46).

**Choice of diuretic.** It is reasonable to begin treatment of congestive heart failure with a thiazide diuretic. Usually, however, a more potent loop diuretic will eventually be needed by patients who have at least moderate heart failure. Attention must be paid to electrolyte imbalance in patients with congestive heart failure because hypokalemia and hypomagnesemia can lead to serious arrhythmias, especially in patients who are taking digitalis. Potassium supplementation is frequently required in patients with congestive heart failure who are taking potent diuretics. Alternatively, a potassium-retaining diuretic might be considered. It should be remembered, however, that the angiotensin-converting enzyme inhibitors retain potassium. Therefore, it is important to discontinue potassium-retaining diuretics and potassium supplementation in patients receiving angiotensin-converting enzyme inhibitors. In patients who become refractory to loop diuretics, one may get additional benefit by adding a thiazide such as metolazone (47). The fact that the two classes of diuretics work at different places in the nephron appears to explain their synergistic effect, which may be quite dramatic in some patients.

**Clinical effect.** Long-term experience has shown that diuretics can be extremely effective in some patients with congestive heart failure. They certainly are required in patients whose peripheral edema and excess fluid retention become major components of the syndrome of heart failure. Although we have no firm data suggesting that diuretics can prolong life in patients with heart failure, it is intuitive that these agents have been beneficial in alleviating symptoms and, in some circumstances, had the appropriate studies been done, they might have been found to have contributed to longevity.

**Inotropic Agents**

**Digitalis**

The most commonly used inotropic agent is digitalis. Numerous questions have arisen over the past few years about the potential benefit of digitalis and have probably led to a decline in its use, particularly in the United Kingdom. In the United States, however, digitalis is still a commonly used agent. It is effective in patients who have atrial fibrillation and a rapid ventricular response. A reduction in the ventricular rate, together with a positive inotropic effect, are generally quite beneficial in these patients. The greatest controversy, however, has arisen about the use of digitalis in patients with congestive heart failure and sinus rhythm. In some studies of such patients discontinuation of digitalis produced no detrimental effects (48,49). In other studies of such patients (50) the patients' heart failure clearly deteriorated (50) after withdrawal of digitalis. In a double blind placebo-controlled crossover study, Lee et al. (51) compared the effects of digoxin and placebo in 25 outpatients with sinus rhythm. In general, there was benefit in patients with a dilated heart, a reduced ejection fraction and a third sound gallop. Other studies with digitalis have also suggested that this drug may be more beneficial in sicker patients as compared with patients with mild heart failure. Dobbs et al. (52) reported a double blind crossover comparison of digi-
Phosphodiesterase Inhibitors

There has been considerable interest in the phosphodiesterase inhibitors, which are potent inotropic agents and vasodilators (58). Inhibition of phosphodiesterase leads to an increase in cyclic adenosine monophosphate (AMP), which enhances calcium entry and thus improves contractility. These agents are also potent peripheral vasodilators, and produce significant hemodynamic effects in patients with heart failure. When given on a short-term basis to patients with heart failure, they result in an increase in cardiac output and a reduction in atrial pressures (59). Similarly, exercise tolerance is increased acutely in most studies (60). Despite these short-term beneficial effects, however, these drugs (amrinone and milrenone) are not yet available for oral use in the United States. Part of the uncertainty regarding their use relates to the long-term effects of these agents, both on exercise tolerance and on mortality (61). Until appropriate studies can clearly define a long-term clinical benefit or a reduction in mortality, these agents are best reserved for patients who have not responded in a beneficial fashion to usual therapy but continue to require some pharmacologic support to maintain an appropriate quality of life or to remain outside of the hospital.

Oral Catecholamines

A number of oral catecholamines have been used in patients with heart failure; these include L-dopa, piributeral, prenalterol and salbutamol (62-65). It appears that these agents can produce short-term beneficial hemodynamic effects. However, a high side effect profile and problems with arrhythmias and potential sudden death have raised serious questions about the use of such agents in patients with congestive heart failure. Intermittent dobutamine in some controlled studies (66) has shown prolonged benefit in such patients. Short-term infusions for 24 to 72 h have been shown to improve both exercise time and ejection fraction over a subsequent period up to 4 weeks. Although the mechanism of this benefit is unclear, a potential training effect has been implicated as has an improvement in mitochondrial function. A recent multicenter study of patients with heart failure treated at home with dobutamine was stopped because of an increase in serious arrhythmias in the treated group. It appears, therefore, that this form of therapy is best administered in a controlled hospital setting.

Overall, it is clear that inotropic agents are much like a double-edged sword; although they can increase hemodynamics and exercise tolerance, their other effects may be potentially harmful to the patient. These include an increase in oxygen consumption, the generation of arrhythmias and the potential for more rapid deterioration of muscle function. It is less certain, therefore, about the long-term role of potent inotropic agents in the management of severe heart failure.

Vasodilator Drugs

Arteriolar Vasodilators

Hydralazine. As illustrated in Figure 4, a major component of the vicious cycle in congestive heart failure is an excess increase in systemic vascular resistance. This increase sets the stage for arteriolar vasodilators, which can decrease systemic resistance and increase cardiac output. Hydralazine is the prototypic agent that has been used in this regard. When administered to patients with severe congestive heart failure, hydralazine increases cardiac output ap-
proximately 50% in association with a concomitant reduction in systemic vascular resistance (67). In general, there is little change or a slight decrease in atrial pressures with hydralazine therapy. This pharmacologic result underscores the reality of the vicious cycle in congestive heart failure, where neurohumoral mechanisms have overshot in their compensatory response and set systemic vascular resistance too high. On the other hand, it is clear that this increase in cardiac output may not necessarily be directed to organs that need it. For example, in a placebo-controlled trial (68) examining the effects of hydralazine on exercise tolerance, hydralazine or placebo was given to patients with moderate heart failure already receiving digitalis and diuretics. Over several weeks there was a slight improvement in the exercise tolerance of the hydralazine-treated patients, but it was no greater than the improvement in exercise tolerance seen in the patients receiving placebo. Thus, this arteriolar vasodilator was effective in increasing cardiac output but ineffective in improving exercise tolerance.

Hydralazine has been used with some effectiveness, however, in unloading the ventricle in patients with volume overload due to valvular regurgitation (69). Hydralazine is effective in both mitral and aortic regurgitation in this regard. In patients who are still asymptomatic but with moderate volume overload due to valvular regurgitation, it seems intuitive that, if one could unload the ventricle, one might delay the rate at which the ventricle dilates and therefore delay the onset of irreversible changes in ventricular function.

In patients with aortic regurgitation it appears that hydralazine may be of some benefit in this regard (70). It should be emphasized, however, that unloading therapy should never act as a substitute for surgical replacement of the valve. When severe changes in contractility occur, they appear to be mostly irreversible.

The effective dose of hydralazine is generally between 200 to 300 mg/day given in divided doses. Hydralazine is metabolized by acetylation. Approximately 50% of the United States population are rapid acetylators and half are slow acetylators. In rapid acetylators, higher doses of hydralazine may be required. Similarly, the lupus syndrome tends to occur primarily in patients who are slow acetylators. The primary side effects of hydralazine are related to the gastrointestinal tract and require discontinuation of this drug in a fair proportion of patients.

Minoxidil. Another potent arteriolar vasodilator that has been evaluated in congestive heart failure is minoxidil, which is approved for the treatment of resistant hypertension. The hemodynamic effects of minoxidil are similar to those of hydralazine (71). The drug produces a substantial increase in cardiac output, together with a minor decrease in atrial pressures. In a placebo-controlled trial (72), however, minoxidil did not increase exercise tolerance as compared with placebo. Side effects included sodium retention and hair growth, the latter being quite troublesome to female patients. Results with these two arteriolar vasodilators suggest a simple but important principle, namely, that arteriolar vasodilators do not increase exercise tolerance, although they are effective in increasing cardiac output.

Venodilators

Nitrates. Nitrates are the prototypic venodilators (73); they are available in many preparations, including sublingual, oral and transdermal. If given in effective doses, they can reduce atrial pressures, presumably by dilating peripheral veins and redistributing blood so that more is in the peripheral veins and less in the chest. When nitrates are given to individuals with normal filling pressures, filling pressures frequently become too low and hypotension and tachycardia result. In patients with congestive heart failure, however, this is not a problem. Nitrates generally do not produce tachycardia in patients with congestive heart failure.

The nitrates have produced an improvement in exercise tolerance in patients with congestive heart failure, as compared with those receiving placebo (74,75). This appears to be true of virtually all agents that lower atrial pressures. Thus, venodilators that lower atrial pressures not only are effective in relieving dyspnea, but also are effective in improving exercise tolerance in patients with congestive heart failure.

Combination therapy. The fact that arteriolar vasodilators can increase cardiac output and that venodilators can reduce filling pressures has led to their combined use in patients with congestive heart failure (76). This combination was able to prolong life in patients with moderate heart failure in the V-HEFT trial (77). This trial was the first trial to demonstrate that vasodilator therapy could prolong life in patients with congestive heart failure and therefore becomes a landmark trial in encouraging physicians to use vasodilators relatively commonly in the management of patients with congestive heart failure.

Nitrates may be used with caution and at lower doses than those used in angina pectoris. The nitroglycerin ointment can be effective in some patients whose dyspnea occurs primarily during the sleeping hours.

Drugs With Combined Arteriolar and Venodilating Effects

Prazosin. The prototypic drug in this category is prazosin, which is an alpha, receptor blocker and can produce
both arteriolar and venous dilation (79). Studies with prazosin have shown that it can reduce filling pressures and increase cardiac output, and thus produce the same hemodynamic effects as those of combined hydralazine and isosorbide dinitrate. Unfortunately, there appears to be a hemodynamic tachyphylaxis with prazosin, such that there are no sustained long-term effects (80). This may explain why prazosin was ineffective in the V-HEFT trial in prolonging life compared with placebo (77). Because of this hemodynamic tachyphylaxis and inability to prolong life, prazosin does not appear to have a role in the management of congestive heart failure as compared with the combination of hydralazine plus isosorbide dinitrate, and the angiotensin-converting enzyme inhibitors.

**Angiotensin-Converting Enzyme Inhibitors**

Captopril, enalapril and lisinopril. These agents have been extremely effective in managing congestive heart failure and appear to represent the vasodilators of choice at present (81). They currently are the three angiotensin-converting enzyme inhibitors available in the United States. The benefit produced by these drugs underscores the concept that the renin-angiotensin-aldosterone system has over-shot in patients with congestive heart failure and can produce adverse hemodynamic effects. It should be remembered that diuretics and arteriolar vasodilators activate this system and thus help to set the stage for the use of angiotensin-converting enzyme inhibitors. The short-term administration of these agents to patients with congestive heart failure produces a reduction in blood pressure and systemic vascular resistance and a striking reduction in left and right atrial pressures. This is accompanied by a modest increase in cardiac output (82). Of some importance is the ability of angiotensin-converting enzyme inhibitors to increase exercise tolerance in patients with congestive heart failure (83). This improvement in exercise tolerance occurs over a period of several weeks, which is different, for example, from the short-term improvement in exercise tolerance that occurs with the potent inotropic agents such as dobutamine or the phosphodiesterase inhibitors (84). More important, this improvement in exercise tolerance appears to be accompanied by an improvement in patient well-being and quality of life. The angiotensin-converting enzyme inhibitors have especially become popular because of their demonstrated effect in prolonging life in the CONSENSUS trial (85). In this trial, patients with severe heart failure (mostly functional class IV) had either an angiotensin-converting enzyme inhibitor (enalapril) or placebo added to their regimen; there was a reduction in mortality in the enalapril-treated group (Fig. 5). A review of some of the captopril data (86) suggests a similar beneficial effect on mortality. It is likely that all of the angiotensin-converting enzyme inhibitors will have generally similar effects, although their short-term effects may be slightly different, in part related to the time course of their action (87).

**Dosage.** An important aspect of the angiotensin-converting enzyme inhibitors is their dose response relation (81). When one has achieved inhibition of converting enzyme, one has reached the appropriate therapeutic dose. This makes it relatively easy to titrate the angiotensin-converting enzyme inhibitors to an appropriate level. One starts with a low dose to avoid or minimize hypotensive effects and then gradually works up to a standard dose. This would be approximately 25 mg three times daily of captopril, 5 to 10 mg twice daily of enalapril and 10 to 20 mg once daily of lisinopril. The newest of these agents, lisinopril, is a long-acting angiotensin-converting enzyme inhibitor and will thus have the advantage of being given only once daily, which may well improve patient compliance (88).
Combination Therapy

Selection of drugs for new onset congestive failure. In the past a step-care approach to the management of heart failure has been suggested. This step-care approach generally included starting with a diuretic and then adding digoxin if necessary. This was followed by the addition of vasodilators if digoxin and diuretics were ineffective together. Recent studies (57), however, have suggested that the vasodilators may be appropriate alternatives to digoxin for first-line therapy. The following approach, therefore, is suggested for patients with new onset congestive heart failure (Table 3). If the patient has evidence of volume excess or systemic or pulmonary edema, it is likely that diuretics will be required as a permanent part of the therapy of these patients. It makes sense, therefore, to start with the diuretics as first-line therapy and then to add other drugs as appropriate. In patients with left ventricular dysfunction or early signs of congestive heart failure, there is important evidence that unloading therapy with the angiotensin-converting enzyme inhibitors may alter remodeling and slow the intrinsic decline in cardiac contractility (12). Thus, vasodilator therapy can be considered much earlier than in the past, and may prove useful in the earliest forms of heart failure to unload the ventricle. On the other hand, digoxin appears to be most effective in patients who have more severe heart failure (51). The benefit of its use in mild heart failure is less certain.

Thus, this approach would consider any of the three classes of drugs as potential first-line therapy in patients with heart failure. Additional classes would be added as needed because of their demonstrated additive effects. For example, digoxin added to captopril has been shown to improve hemodynamics in patients with congestive heart failure (89). Similarly, hydralazine as an arteriolar vasodilator when added to captopril has been shown to be beneficial in further improving cardiac output (90).

Effect on survival. In selecting drugs one must remember that only the vasodilators have shown a prolongation of life in placebo-controlled trials (91). In the V-HEFT trial, the combination of hydralazine plus isosorbide dinitrate was effective in prolonging life in the treatment group as compared with the patients receiving placebo or prazosin (77). All had moderate heart failure and baseline therapy of digitalis and diuretics. In the CONSENSUS trial (85) enalapril was effective in prolonging life in patients with severe heart failure (Fig. 5). Thus, vasodilators have been shown to prolong life in patients with both moderate and severe heart failure. Because of their potential benefit in mild heart failure, or even in left ventricular dysfunction, it appears that a vasodilator regimen may emerge as core therapy for patients with all stages of congestive heart failure. Because of their potential beneficial effects they should be used in patients with severe heart failure unless there are contraindications such as renal insufficiency.

Hemodynamic effects. In virtually all studies in which combination therapy with different classes of drugs has been used, it appears that their hemodynamic effects are generally additive. Thus, in patients with severe heart failure it makes good sense to consider the combination of diuretics, inotropic agents and vasodilators to maximize beneficial hemodynamic effects. This is conceptually shown in Figure 6. In general, therefore, one can start with any of the classes of drugs as suggested above and then gradually add other classes as the heart failure worsens so that patients are eventually receiving all three types of antifailure therapy.

Antiarrhythmic Drugs

The mode of death in patients with severe heart failure is sudden approximately 40% of the time (5). Studies (92) with Holter electrocardiographic (ECG) monitors in patients with congestive heart failure have demonstrated that arrhythmias occur in approximately 90% of patients and that non-sustained ventricular tachycardia or multifocal premature ventricular complexes are relatively common. The data suggest that arrhythmias add independently to an adverse prognosis in patients with congestive heart failure (93), although the level of left ventricular dysfunction remains the most important adverse prognostic factor. It has therefore been reasonable to consider some form of antiarrhythmic therapy in patients with severe heart failure and associated serious arrhythmias. The value of this therapy is uncertain at present. The following discussion represents potential directions that one might take until more definitive data are available.

Reduction of proarrhythmic factors. It seems prudent initially to reduce or eliminate all proarrhythmic factors (94) that can be recognized (Table 4). These might include adverse effects of inotropic agents, such as digitalis in the presence of hypokalemia. Electrolyte imbalance should be
patients with excess arrhythmias. The mechanism of re-

tricular complexes in patients with severe heart failure

reduced premature ventricular complexes with the angioten-

the CONSENSUS trial (85) it still may be that reduction of

converting enzyme inhibitors could be of benefit in some

which could also decrease episodes of ischemia; and a

tricle, which may reduce stretch-induced arrhythmias or

physician must make a decision whether to treat the arrhyth-

mnia. One must remember that, in general, antiarrhythmic

therapy has a proarrhythmic effect that is seen in approxi-

mately 10% of patients, a figure that may, in fact, be closer to

20% in patients with severe heart failure (94). In addition,

studies (95) have shown that the efficacy of antiarrhythmic

agents appears to be proportionally less as the degree of heart

failure increases. At the present time, we do not have any

placebo-controlled trials to suggest that antiarrhythmic ther-

apy can prolong life, although such trials are either underway

or in the planning stage. The physician is therefore left to his

best judgment in regard to antiarrhythmic therapy.

<table>
<thead>
<tr>
<th>Table 4. Proarrhythmic Factors in Congestive Heart Failure</th>
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<tbody>
<tr>
<td>1. Arrhythmogenic effects of positive inotropic agents</td>
</tr>
<tr>
<td>2. Electrolyte imbalance</td>
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<tr>
<td>3. Ischemia</td>
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<tr>
<td>4. High catecholamines</td>
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<tr>
<td>5. Myocardial damage</td>
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<tr>
<td>6. Myocardial stretch</td>
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<tr>
<td>7. Hypotension</td>
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<tr>
<td>8. Proarrhythmic effects of antiarrhythmic agents</td>
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corrected wherever possible. Ischemia can be an important

contributory factor to prognosis, and can be treated with

appropriate anti-ischemic agents such as nitrates. High cat-

echolamine levels may also contribute to arrhythmias. In

patients with severe heart failure it would be difficult to

consider using beta-blockers or calcium channel blockers as

antiarrhythmic agents, although such therapy could be used in

patients with less severe congestive heart failure. Because of

the evidence that increased stretch might play a role in

producing arrhythmias in heart failure, vasodilator therapy

may be helpful in eliminating this proarrhythmic factor.

Placebo-controlled trials with the angiotensin-converting en-
zyme inhibitors have shown a reduction in premature ven-

tricular complexes in patients with severe heart failure

(57,85). Although there was no reduction in sudden death in

the CONSENSUS trial (85) it still may be that reduction of

premature ventricular complexes with the angiotensin-

converting enzyme inhibitors could be of benefit in some

patients with excess arrhythmias. The mechanism of re-

duced premature ventricular complexes with the angioten-

sin-converting enzyme inhibitors is unknown. Factors that

might contribute, however, would include an increase in

serum potassium, which is frequently seen with the angio-

tensin-converting enzyme inhibitors; unloading of the ven-

tricle, which may reduce stretch-induced arrhythmias or

ischemia; a decrease in myocardial oxygen consumption, which

could also decrease episodes of ischemia; and a

withdrawal of sympathetic tone. These or other factors may

contribute to this beneficial antiarrhythmic effect.

*Indications for antiarrhythmic therapy.* When all pro-

arrhythmic factors have been ruled out and a patient with

congestive heart failure still has serious arrhythmias the

physician must make a decision whether to treat the arrhyth-

mia. One must remember that, in general, antiarrhythmic

therapy has a proarrhythmic effect that is seen in approxi-

mately 10% of patients, a figure that may, in fact, be closer to

20% in patients with severe heart failure (94). In addition,

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apy can prolong life, although such trials are either underway

or in the planning stage. The physician is therefore left to his

best judgment in regard to antiarrhythmic therapy.

Effect on survival. In a retrospective review (96) of the
data in a group of patients whom we treated with potent oral

inotropic agents (phosphodiesterase inhibitors) we noted

that sudden death appeared to occur less often in patients

treated with antiarrhythmic agents as those in patients not so

treated. Cleland et al. (97) also suggested that the drug

amiodarone may be effective in prolonging life in patients

with severe heart failure and arrhythmias. Although such
data are uncontrolled, they do suggest the possibility that

antiarrhythmic drugs may be of some benefit. Certainly the

toxic effects of amiodarone become less important in pa-

tients with severe heart failure when life span is generally

shortened. Until well controlled studies are available, how-

ever, physician judgment must be used in the absence of firm
data in determining whether to use antiarrhythmic therapy in

selected patients.

Summary

*In conclusion,* we have learned a tremendous amount

about the pathophysiology of congestive heart failure over

the past 2 decades. One of the most important principles

that has emerged is that compensatory mechanisms that are

initially helpful may subsequently become deleterious. Counter-

acting these compensatory mechanisms has formed one of the

most important therapeutic approaches to patients with con-

gestive heart failure. Of the three classes of drugs available

to treat congestive heart failure, the vasodilator drugs have

emerged as the most important, especially because of their

demonstrated ability to prolong life. Of the available vasodi-
lator drugs, the angiotensin-converting enzyme inhibitors

have emerged as the most important single class of drugs to

consider in patients with heart failure. Because of the additive

effects of all three classes of drugs, it is reasonable to start

with one agent and then sequentially add others as required so

that most patients with severe heart failure will be receiving a

combination of a diuretic, an inotropic agent and a vasodilator

drug. The role of antiarrhythmic agents is not settled as yet,

although the prevalence of severe arrhythmias and sudden

death suggests the possibility that these agents may be of

benefit to some patients with congestive heart failure and

serious arrhythmias.

In looking to the future, it is clear that prevention of heart

failure should be one of our most important goals as physi-
cians. As with any disease, preventive measures are far

more effective in the long run than is treating the end stage of

the disease. Because coronary artery disease is the most

common cause of congestive heart failure in the United

States, preventive measures will be closely linked to the

ability to control and alter risk factors in a way that will

reduce the incidence of coronary disease and the damaging

effects of myocardial infarction. Revascularization proce-
dures both during acute infarction and in chronic coronary

disease may also delay the adverse effects of myocardial
damage in this syndrome. Unloading agents early in the course of left ventricular dysfunction may also prove to be an effective way to delay the onset of heart failure. It is likely that this emphasis on prevention will, over time, produce greater benefit than the current benefit seen with the use of drugs in patients with established congestive heart failure.

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