Current Therapy of the Failing Heart

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New concepts regarding pathophysiology of heart failure and new approaches to its management have been prominent in the cardiology literature during the last decade. Data provided from a multitude of clinical studies have yielded new insights into the syndrome of heart failure and have focused our attention on problems still in need of solution. The purpose of this review will be to assess the current state of our knowledge regarding the management of heart failure and to develop a rational treatment strategy. Emphasis will be given to those areas where therapy still is controversial.

Definition of Heart Failure

Considerable controversy exists regarding an appropriate operational definition for the syndrome associated with the failing heart. Use of the term “congestive heart failure” may be criticized because fluid retention and circulatory congestion (the classic “backward failure”) does not necessarily coexist with deficiency of cardiac function or impaired response of cardiac output to exercise (the classic “forward failure”). Thus, limiting the diagnosis of heart failure to the presence of congestive signs or symptoms may exclude clinical syndromes that should be defined as heart failure.

A traditional physiological definition of heart failure is that it represents a syndrome in which cardiac output does not keep pace with the peripheral demands for blood flow. This definition does not provide a clinically useful diagnostic criterion and also suggests incorrectly that the cardiac output is always low in heart failure.

A more useful contemporary definition of heart failure is that it is a syndrome in which cardiac dysfunction is accompanied by reduced exercise tolerance. This definition provides the physician with diagnostic criteria but is perhaps too narrow in its content. A more comprehensive definition might be that heart failure represents a syndrome in which cardiac dysfunction is associated with reduced exercise tolerance, a high incidence of ventricular arrhythmias, and shortened life expectancy (Figure 1). Thus, the clinical heart failure syndrome represents a subset of populations with left ventricular dysfunction, exercise intolerance, and ventricular arrhythmias. The majority of sudden death occurs in the setting of ventricular dysfunction and usually with coexisting heart failure.

All definitions of heart failure include a criterion of abnormal cardiac performance. In the absence of primary valve dysfunction or of obstruction to inflow or outflow, this impairment of cardiac performance can be related to abnormal muscle function. The quantitation of this cardiac dysfunction is more controversial. Systolic dysfunction is most commonly assessed by the measurement of left ventricular ejection fraction. Such a measurement of course would exclude instances of pure right ventricular failure. It is now clear that symptoms of heart failure may exist in the absence of demonstrable abnormalities of systolic performance because of the presence of disturbed diastolic function of the ventricle. Quantitation of this diastolic dysfunction is still difficult. In addition, measurements of ventricular function made at rest may be misleading because they may fail to detect the abnormal response of the ventricle to the stress of exercise. Because symptoms of heart failure occur predominantly during exercise, quantitation of ventricular systolic and diastolic function during exercise would ideally serve as the “gold standard” for assessment of ventricular function in patients with heart failure. Because such measurements are currently not clinically applicable, the definition of ventricular dysfunction as a guide to the diagnosis of heart failure must remain somewhat subjective. In addition, the poor correlation noted between left ventricular systolic function and exercise tolerance makes it difficult to attribute reduced exercise capacity directly to impaired ventricular performance.

The recognition that left ventricular dysfunction can coexist with normal exercise tolerance has led to an interest in therapy that might be viewed as preventive rather than therapeutic. Although this syndrome may represent the earliest stage of heart failure, therapy to prevent the development of symptoms and of exercise intolerance has not yet been proved to be effective. The term “heart failure” probably should not be used to refer to these patients if they are asymptomatic and if formal exercise testing confirms normal performance. A more appropriate diagnostic term for this group of patients would be “syndromes that may represent an earliest stage of heart failure.”
individuals is "asymptomatic left ventricular dysfunction." One caveat, however, is that some of these patients may have subtle symptoms that adversely affect their quality of life without necessarily reducing their peak exercise capacity.

Severity of Heart Failure

Classification of the severity of heart failure depends on the criteria used and the therapy at the time of classification. Terms such as "mild" and "severe" are often used without rigorous definition. The New York Heart Association functional classification is often used, but this schema is not very discriminating and is dependent on the patient's report of limitation of exercise capacity without adequate regard to his or her life-style.

The role of therapy in altering the clinical severity of the disease cannot be disregarded. For example, the patient in pulmonary edema with severe symptomatology may be made almost asymptomatic by diuretic therapy. Is this patient's heart failure mild, New York Heart Association Class II? Or is it severe, New York Heart Association Class IV, as it would likely be without treatment?

Because the syndrome has several components (ventricular function, exercise tolerance, and arrhythmias) and all of these variables may influence survival, it seems reasonable to define severity in more specific terms. For example, a patient with a left ventricular ejection fraction of 15% might be classified as severe from the standpoint of ventricular function, but if his or her exercise tolerance is only slightly reduced he or she may be classified as mild from that standpoint. Because classification of severity is of importance predominantly in planning therapy and assessing prognosis and because the prognosis and goals of therapy would vary depending on the degree of impairment of each of the variables, such a classification schema might be useful in clinical management.

Goals of Therapy for Heart Failure

There can be only two goals in the management of heart failure: to relieve symptoms and improve the quality of life and to prolong life. Effective therapy, therefore, should accomplish at least one of these goals. We shall explore the various therapeutic endpoints that have been used as surrogates for these goals and assess our present knowledge about the effectiveness of the various therapeutic modalities in achieving these endpoints.

Correlates of Symptoms and Quality of Life

Hemodynamics. Because a low cardiac output and a high cardiac filling pressure are the hemodynamic hallmarks of heart failure and are thought to be the major circulatory determinants of the fatigue and breathlessness that characterize heart failure, it has been assumed that drug therapy that favorably influences the cardiac output and cardiac filling pressure should relieve symptoms in patients with heart failure. In patients with severe decompensated heart failure in coronary care units, it is clear that acute restoration of the low cardiac output or of the elevated pulmonary capillary wedge pressure can strikingly relieve the symptoms of severe pump failure. The dramatic evidence that this favorable hemodynamic effect can be achieved by the intravenous infusion of either a potent vasodilator drug, such as sodium nitroprusside, or of a potent inotropic drug, such as dobutamine, or their combination, has led to the perhaps oversimplified concept that chronic maintenance of this improved hemodynamic state should be accomplished by relief of symptoms of chronic heart failure. A variety of oral drug regimens including vasodilators such as isosorbide dinitrate, hydralazine, converting enzyme inhibitors, prazosin, minoxidil, nitrendipine, and other calcium antagonists and many oral positive inotropic drugs such as amrinone, milrinone, enoximone, piroximone, and ARL 115BS all appear to have had a favorable chronic effect on left ventricular hemodynamics. Despite these hemodynamic effects, not all of these agents appear to have had a favorable influence on symptoms or quality of life.

Exercise tolerance. Exercise intolerance is the major complaint of most patients with heart failure; therefore, it is only natural that exercise testing would come to form an important therapeutic endpoint to evaluate the efficacy of treatment. A major
limitation with this quantitative exercise testing is that the protocol used to measure exercise capacity may not adequately reflect the impaired exercise performance that limits the patient’s activity level. Most tests used to evaluate patients with heart failure begin at low workloads and increase gradually with time until the patient reaches his maximal capacity to perform work. When this progressive maximum exercise test is carried out during gas exchange measurements, a peak oxygen consumption (VO₂) can be measured.

A further advantage of gas exchange measurements is that monitoring of expired O₂ and CO₂ provides evidence that the patient has approached maximum exercise tolerance by surpassing the anaerobic threshold. Indeed, changes in the workload required to reach the anaerobic threshold could possibly serve as a metabolic marker for a change in exercise tolerance.

A reduction of peak exercise performance or, more precisely, a reduction of peak oxygen consumption to less than 20–25 ml/kg/min has been used in recent years as a criterion for entrance into many clinical trials of therapeutic interventions in heart failure. Although this impaired exercise performance may identify patients whose ventricular dysfunction has become symptomatic, there is yet no compelling evidence to support the view that a therapeutic response in terms of peak exercise performance will necessarily be accompanied by relief of symptoms or, on the other hand, that the failure of improvement of peak exercise performance indicates no improvement in symptoms of heart failure.

Many drug regimens have been demonstrated to improve peak exercise capacity in patients with heart failure. These include isosorbide dinitrate, captopril, enalapril, a combination of hydralazine and isosorbide dinitrate, furosemide, and some of the newer positive inotropic drugs.

Quality of life. A more global assessment of patient symptomatology has resulted from attempts to use questionnaires to assess quality of life. A variety of instruments have been used in this endeavor, and new questionnaires have recently been developed to address more specifically life quality in patients with heart failure. Early results with these questionnaires have suggested that they appear to be measuring something that correlates only poorly with exercise tolerance itself and that the scores in individual patients can be improved by therapeutic interventions.

Predictors of Mortality

Ejection fraction. Noninvasively determined left ventricular ejection fraction has proved to be a powerful predictor of mortality in patients with heart failure. The correlations observed in many clinical trials have raised the possibility that an improvement in ejection fraction might have a favorable influence on long-term survival. The problem with this hypothesis is that the low ejection fraction in chronic heart failure represents not only the reduced systolic function of heart failure but also the consequence of a prolonged increase in ventricular wall stress and plastic remodeling of the left ventricle. Thus, improved left ventricular systolic performance may not necessarily result in normalization of the ejection fraction.

Nonetheless, ejection fraction has often been used as one of the therapeutic endpoints in heart failure studies. Hydralazine and isosorbide dinitrate combination therapy has been demonstrated to improve ejection fraction as has captopril in some trials but not in others. In a recent study, digoxin has been demonstrated to have a significantly favorable effect on ejection fraction. Some of the newer oral phosphodiesterease inhibitor inotropic agents have also been demonstrated to improve ejection fraction. Although this favorable effect on ejection fraction might be used as a surrogate for an improvement in mortality, it is premature to make that simple assumption.

Arrhythmias. Frequent premature ventricular contractions and asymptomatic runs of ventricular tachycardia are characteristic of the syndrome of heart failure. Holter monitoring in these patients often reveals bizarre electrical instability that often leads physicians to institute antiarrhythmic therapy. In the absence of symptoms from the arrhythmia, such antiarrhythmic therapy probably is not prudent because these patients also are at particularly high risk to experience a proarrhythmic effect of an antiarrhythmic drug. These agents have been demonstrated to suppress the ventricular arrhythmias, but their usefulness in preventing sudden death in heart failure remains unproved.

Sudden death represents a common terminal event in patients with heart failure, and results of early clinical studies have failed to demonstrate an intervention that can strikingly reduce this high mortality rate. Sometimes, amiodarone, the Type III antiarrhythmic drug, appears to have the potential to prolong life in patients who suffer from recurrent runs of ventricular tachycardia. If these antiarrhythmic drugs are to become a common component of the management of heart failure, then the appropriateness of this therapeutic intervention should be determined by careful study of a representative population and a representative array of antiarrhythmic drugs. Such a study is currently underway within the National Heart, Lung, and Blood Institute (CAST, the Cardiac Arrhythmia Suppression Trial), but the patient population in this study is not necessarily one with symptoms of heart failure.

Neurohormonal activity. Activation of the sympathetic nervous system, the renin angiotensin aldosterone system, and the antiuretic hormone vasopressin system is a common manifestation of heart failure. The degree of activation of the sympathetic nervous system as measured by plasma norepinephrine concentration has appeared to serve...
as a sensitive predictor of mortality.\textsuperscript{23} Patients with a plasma norepinephrine concentration of more than 600 pg/ml, indicative of activation of the sympathetic nervous system, have much shorter life expectancies than those whose plasma norepinephrine is less than 600 pg/ml.\textsuperscript{24} This observation of the apparent sensitivity of plasma norepinephrine as a marker for the severity of the disease has led to the use of this plasma assay as a possible surrogate for improvement in the syndrome and reduction of the risk of mortality. The appropriateness of this measurement as a guide to therapeutic response has yet to be validated.

Plasma renin activity also serves as a useful marker of disturbed pathophysiology in patients with heart failure, but it appears to be more variably stimulated in heart failure and more closely associated with acute decompensation and the use of potent diuretic therapy. A low serum sodium, which in itself may portend a poor prognosis, may be used as a predictor of a high plasma renin activity in patients with heart failure.\textsuperscript{25} Improvement of the clinical syndrome with restoration of serum sodium to normal should, therefore, be accompanied by a reduction of plasma renin activity. Although a high plasma renin activity might imply a favorable response to converting enzyme inhibitors, and the acute hemodynamic response to these drugs is more dramatic in that clinical setting,\textsuperscript{25,26} long-term clinical response to these drugs appears not to depend on a high plasma renin activity when therapy is initiated. This observation appears to confirm previous experience in the treatment of essential hypertension with these drugs in which a high plasma renin activity is not a prerequisite for a favorable long-term antihypertensive effect.

Mortality rate. Heart failure carries with it a grim prognosis dependent on the severity of the syndrome as assessed by left ventricular ejection fraction and exercise tolerance as well as other baseline variables. In a variety of clinical trials, mortality rate in heart failure has ranged from approximately 10\% a year to as high as 50\% a year. Attempts to reduce this high mortality rate have been the focus of many recent multicenter clinical trials. In patients with mild-to-moderate heart failure (New York Heart Association Class II and Class III), therapy with hydralazine and isosorbide dinitrate added to digoxin and diuretics has been demonstrated to reduce mortality (38\% reduction at 1 year, 25\% at 2 years) when compared with a placebo or prazosin added to digoxin and diuretic therapy.\textsuperscript{16} In Class IV heart failure, addition to conventional therapy of the converting enzyme inhibitor enalapril has been demonstrated to reduce mortality (31\% reduction at 1 year) when compared with addition of a placebo.\textsuperscript{27}

Concern also has been raised that some therapies, particularly the phosphodiesterase-inhibiting inotropic-vasodilator drugs, might relieve symptoms of heart failure but actually shorten life expectancy.\textsuperscript{28} However, none of the studies of these agents has been large enough to demonstrate either a favorable or an unfavorable effect on mortality.

Therapy of Heart Failure

Many nonpharmacological and pharmacological approaches to management of the patient with heart failure are now available. Optimal use of these therapies requires an assessment of the severity of the syndrome, the therapeutic goals, and the disturbed pathophysiology in the individual patient.

Correction of Cause of Ventricular Dysfunction

The most common correctable cause of myocardial dysfunction is ischemia, which may be silent in terms of chest pain and may produce prolonged regional depression of ventricular function. When reversible ischemia is a possible factor in heart failure, even if global ventricular function is severely depressed, evaluation for possible reperfusion procedures clearly is indicated. Unfortunately, no single technique can reliably distinguish "stunned" or "hibernating" myocardium from scarred myocardium.

Cardiac depressants also may precipitate heart failure. The most common possible offenders are alcohol, antiarrhythmic drugs, \(\beta\)-adrenoceptor antagonists, and calcium antagonists. Alcohol intake should be severely restricted and cardiac-depressant drugs withheld, if possible, in patients with failing hearts. \(\beta\)-Blockers will be discussed further below.

Diet

Because most patients with heart failure have impaired renal excretory capacity for sodium, restriction of sodium intake is an important component of therapy. The availability of potent diuretic agents may reduce the dependence of the patient on rigid salt restriction, but attempts to reduce sodium intake to less than 2 g/day should be an important part of management. Of particular importance is the avoidance of binge salt eating that may lead to acute circulatory congestion and episodes of decompensation. Such episodes of acute cardiac dilatation can have an adverse effect on left ventricular function that may long outlast the circulatory congestion.

Exercise

Traditional advice to the patient with heart failure has been to avoid exercise and maintain a sedentary existence. It is now clear that such striking restriction of exercise leads to deconditioning that may adversely affect exercise tolerance. Careful exercise training in patients with heart failure can augment peak exercise capacity and can improve the comfort with which submaximal exercise can be carried out. What is not yet proved is whether this improvement in exercise capacity can be accomplished without having an adverse effect on prognosis of the syndrome by virtue of some aggravation of ventricular dysfunction by chronic increases in workload. Until evidence to the contrary is pre-
sented, however, it seems appropriate to encourage patients with heart failure to maintain exercise levels within their exercise capacity to avoid the deleterious effects of deconditioning. Such exercise probably should be in the form of isotonic activity such as vigorous walking or bicycling rather than the isometric exercise of activities such as weight lifting. Such encouragement of exercise should, of course, be withheld until acute symptoms of heart failure have been relieved and circulatory congestion has been controlled.

Diuretics

In the sodium-retaining patient whose cardiac filling pressures cannot be maintained within normal limits by salt restriction alone, diuretics become a necessary component of the therapeutic armamentarium. The goal of diuretic therapy is to normalize cardiac filling pressure, not merely to relieve edema. Thus, the indications for diuretic therapy and the adjustment of diuretic doses is dependent on direct or indirect assessment of the level of cardiac filling pressure. This can be accomplished for the right ventricle quite accurately by measuring the peak of the jugular venous pressure wave in the neck. The augmentation of this jugular venous pressure by right upper quadrant abdominal pressure or by exercise can serve as a guide to the adequacy of diuretic therapy. The left atrial pressure is more difficult to assess clinically in the absence of right heart catheterization and, thus, must be assessed indirectly by lung examination, chest x-ray, and symptoms. When dyspnea on exertion is not accompanied by other signs of circulatory congestion but the possibility of a rise in pulmonary capillary pressure during exercise is considered, a trial of diuretic therapy and assessment of effect on exercise tolerance may be appropriate.

Diuretic therapy may be initiated with intermittent doses of thiazide diuretics that may be required no more often than two or three times weekly. If intermittent mild diuretic therapy is ineffective in maintaining cardiac filling pressures at normal levels, then a more regular schedule of diuretic therapy and a switch to a more potent loop diuretic such as furosemide may be necessary. For more resistant circulatory congestion, addition of a distally active agent such as metolazone to furosemide is more effective than further increases in the dose of furosemide. Once diuretic therapy has been initiated, adjustment of the dose should be made on the basis of daily weight supplemented by periodic estimations of the central venous pressure and of pulmonary symptoms. Self-adjustment of diuretic therapy by the compliant patient may be appropriate on the basis of changes in body weight measured at home. These fine tuning adjustments of diuretic therapy may help to keep the patient at dry weight and avoid either the circulatory congestion or the volume depletion that may lead to symptoms of acute decompensation. Supplementation of potassium or administration of a potassium-retaining diuretic is an important part of diuretic therapy. When only occasional diuretic usage is required, serum potassium usually does not fall, but if daily doses of diuretics become necessary, it usually is necessary to monitor serum potassium and provide appropriate dietary or pharmacological therapy. Although concomitant use of angiotensin-converting enzyme inhibitors usually reduces the need for potassium supplementation or potassium-retaining diuretics, some patients with severe heart failure who require daily furosemide doses remain hypokalemic even in the presence of converting enzyme inhibition. Cautious potassium administration may be necessary in such patients, but close monitoring of serum potassium is required.

Vasodilators

Vasodilator drugs now should be considered a standard part of therapy for patients with symptomatic heart failure. Indeed, diuretics probably should never be used alone in such patients but should always be accompanied by the coadministration of a vasodilator. Isosorbide dinitrate represents the simplest vasodilator. Its venodilator effect results in a striking fall in cardiac filling pressure that can complement diuretics in lowering right atrial and left atrial pressures. Considerable controversy has grown in recent years regarding the question of tolerance to the vascular effects of nitrates administered chronically. In some studies, the arterial vasodilating effect of nitrates has been demonstrated to wane after short-term exposure to a nitrate.29 In other studies, however, vascular effects can be shown to persist, particularly when the nitrate is administered so that a constant blood level is not achieved.30 Isosorbide dinitrate is the best studied of these nitrates and when administered orally in doses of 20–60 mg three or four times daily the hemodynamic effect appears to, at least in part, persist and clinical benefits of chronic therapy can be demonstrated.

In most instances, administration of a nitrate should be accompanied by the administration of an arterially active vasodilator that more effectively increases cardiac output.31 Hydralazine is the agent most frequently used for this purpose and when given in doses of 150–300 mg/day appears to have a synergistic effect with isosorbide dinitrate in increasing cardiac output, lowering cardiac filling pressure, improving exercise tolerance, and prolonging life. The major side effects of the combination of isosorbide dinitrate and hydralazine are headaches that often force reduction of the dosage. Some patients find even small doses of the nitrate intolerable, and in these instances, alternate vasodilator therapy should be sought.

The converting enzyme inhibitors, captopril and enalapril, have gained wide popularity in the management of heart failure because of their demonstrated hemodynamic and clinical efficacy. These
drugs exert a prominent effect on the right and left atrial pressures and a modest increase in cardiac output. In most studies, captopril (75–150 mg/day) or enalapril (10–20 mg/day) have been effective in improving exercise tolerance and relieving the symptoms of heart failure. Therapy with these drugs is preferably initiated at lower doses to avoid a prolonged hypotensive effect that may occur in volume-depleted or high-renin patients. When administered with diuretics, the angiotensin-converting enzyme inhibitors minimize the loss of serum potassium and avoid the reflex renin-angiotensin stimulating effect of diuretic therapy. Because recent trials have demonstrated a life-prolonging effect of converting enzyme inhibitors and of hydralazine-nitrate combination, either of these regimens may be administered with a goal of reducing long-term mortality.

A variety of other vasodilators have been used in patients with heart failure, but these other drugs have not been as uniformly effective. Prazosin exerts an acute hemodynamic effect that may not be as well sustained during chronic therapy. In the V-HeFT trial, prazosin had no effect on survival when compared to a placebo. Therefore, this agent should probably not be a vasodilator drug of choice in heart failure. Similarly, minoxidil when used alone, does not have a favorable effect on the clinical syndrome, although it improves hemodynamics. Calcium antagonists also have been noted to improve hemodynamics, but large-scale control trials have not been carried out to demonstrate whether this hemodynamic effect is accompanied by any improvement in exercise tolerance or quality of life.

**Digitalis**

Considerable controversy has grown in recent years regarding the efficacy of digoxin in the management of heart failure with a normal sinus rhythm. In at least two recent studies, digoxin has proved to have a favorable effect on some aspect of the clinical syndrome of heart failure when compared with a placebo. In one study, digoxin significantly increased left ventricular ejection fraction, whereas in another study digoxin appeared to improve exercise tolerance. In both studies, symptoms of heart failure were relieved, and complications of heart failure were reduced.

Efficacy of digitalis in heart failure appears to be most clearly demonstrable in patients with more severe symptoms and more dilated left ventricles. Thus, a low ejection fraction accompanied by an S3 gallop and more severe symptoms of heart failure would clearly be an indication for administration of digoxin. Even earlier administration of the drug in patients with modest reduction of ejection fraction might be appropriate with the hope that an improvement of ejection fraction might have a favorable long-term effect on the disease. Such evidence is still lacking, however.

Concern about the possible arrhythmogenic effects of digoxin in patients with heart failure has been generated by the suggestion that digoxin therapy is associated with shortened life expectancy in a post-myocardial infarction population. Although the results of these observations have been contradicted by other studies, that digoxin could precipitate lethal arrhythmias in patients with heart failure who are already prone to such arrhythmias is a possibility. Careful attention to serum potassium and careful avoidance of overdoses of digitalis is mandatory. A well-controlled prospective mortality studies would be necessary to eliminate the possibility of an adverse potential for digitalis in patients with heart failure.

**New Inotropic Drugs**

The hope that new orally effective inotropic drugs would emerge to replace or supplement digitalis in the management of heart failure has not yet been realized. The phosphodiesterase inhibitors milrinone and amrinone have been approved for intravenous use in the management of acute pump failure, but the oral forms of these drugs have not received FDA approval because of the failure to demonstrate clinical efficacy and safety. Other inotropic drugs are currently under investigation, some with pharmacological actions similar to those of milrinone but others with different and often unique mechanisms of action. Clinical trials of these drugs will be required to demonstrate not only a favorable hemodynamic effect, which already is clear with most of these compounds, but also an improvement of exercise tolerance, an improvement of quality of life, and evidence that they do not have an adverse effect on survival.

**β-Adrenoceptor Blockers**

Recent suggestions that careful titration of β-blocker therapy can have a favorable influence on symptoms and the natural history of heart failure have led to the initiation of a controlled clinical trial to evaluate this form of treatment in patients with cardiomyopathy. Although the traditional view has been that β-receptor activity is essential to the maintenance of cardiac performance in patients with depressed left ventricular function, the preliminary studies with β-blockers suggest that, at least in a subset of the patient population, careful titration of these drugs can be accomplished without a significant adverse effect on circulatory function. Furthermore, long-term effects appear favorable in this subset of the patient population. The mechanism of the possible favorable effect of β-blockers is not clear but may relate to alterations in β-receptor density or sensitivity and/or to slowing of the heart rate and improvement of ventricular diastolic function.

**Transplantation**

Heart transplantation has now become a standard aggressive form of management for patients with
heart failure. Survival rates in transplant recipients now approaches 95% over 2 years, and improved quality of life and return to active employment is almost universal in this patient population. This remarkably favorable long-term response to this treatment has led to consideration of earlier intervention in patients with severe ventricular dysfunction who are likely to deteriorate. This enthusiasm for aggressive use of heart transplantation has been tempered by the limited availability of donor organs and the long waiting lists that currently exist at most successful centers.

As the results of heart transplantation have improved and the immunosuppressive regimens have become more precisely monitored and better tolerated, the age and concomitant disease restrictions for the transplant recipient have been relaxed. Thus, patients are now accepted into some transplant programs up to the age of 65 and the presence of diabetes is not necessarily a contraindication. Nonetheless, limited donor availability again leads to the inevitable approach favoring the younger and healthier individual who might have a longer period of productivity after his or her heart transplantation.

An Algorithm for Therapy

A logical approach to the evaluation and pharmacological management of ventricular dysfunction is outlined in Figure 2. The sequence is initiated by the suspicion of ventricular dysfunction that cannot be attributed to organic obstructive lesions, hypertension, or reversible myocardial ischemia. A key to the algorithm is evaluation of ventricular chamber size (increased end-diastolic volume and/or reduced ejection fraction), which can be quantitated by echocardiographic or radionuclide imaging procedures. Enlargement of both the left- and right-sided chambers implies an advanced stage of heart failure with congestive symptoms. Treatment for this syndrome would usually include vasodilators, digoxin, and diuretics. When dilatation is confined to the left ventricle, symptoms may or may not be present. In the presence of symptoms, vasodilators and digoxin would be appropriate agents to improve ventricular function, and diuretics should be used only to relieve congestive symptoms. Patients without symptoms would currently not warrant therapy; however, two multicenter trials are currently addressing this question. Management of patients with isolated right-sided dilatation or the suspicion of a decrease in ventricular compliance as a cause of these symptoms is far less satisfactory. Quantitation of diastolic dysfunction to identify the subset of patients with a predominant problem of reduced ventricular compliance is difficult, and the diagnosis often is made indirectly by demonstration of a high cardiac filling pressure with a normal chamber size. Agents to improve ventricular diastolic function (calcium antagonists or β-blockers) may be used in an attempt to improve left ventricular filling. The

![Diagram](http://circ.ahajournals.org/)

**Figure 2.** An algorithm for pharmacological treatment of left ventricular dysfunction. (See text for details.)
search also continues for a selective pulmonary vasodilator to produce a sustained reduction in impedance to right ventricular emptying in the setting of pulmonary vascular disease or predominant right ventricular failure.

The therapeutic principles are quite simple. Vasodilators and digoxin are indicated whenever the left ventricle is dilated and systolic emptying is reduced. Diuretics are used only as needed to reduce an elevated cardiac filling pressure.

**Secondary Prevention of Heart Failure**

Therapeutic efficacy of the various pharmacological agents available and their prudent use has now made relief of symptoms and an improvement of the quality of life a practical goal in most patients with heart failure. The evidence from recent mortality trials that vasodilator therapy can significantly prolong life has established the concept that loading conditions on the left ventricle can have a long-term deleterious effect on ventricular function and contribute to shortened life expectancy. This evidence for a favorable effect of interventions aimed at the periphery and not at the myocardial process itself has raised the possibility that aggressive early attempts at reducing loading conditions on the ventricle can have a favorable influence on long-term prognosis. It is not clear whether this favorable effect is accomplished simply by reducing myocardial preload and afterload or whether it results from some more subtle long-term effects on the myocardium. Many factors could contribute to progressive change in the structure and/or function of the ventricular myocardium (Table 1). A possible role for these biochemical or physiological effects in the progression of heart failure needs further study.

The poor prognosis in patients with symptomatic congestive heart failure certainly encourages more aggressive attempts to prevent progression of myocardial dysfunction rather than to wait for symptoms to treat. Two intervention trials currently in progress are addressing the possibility that preventive therapy before the onset of symptoms can have a favorable long-term effect. One of these studies is the National Institutes of Health–sponsored Study of Left Ventricular Dysfunction (SOLVD), and the other is the pharmaceutical company–sponsored Study of Survival and Ventricular Enlargement (SAVE). Both of these studies are using a converting enzyme inhibitor, the former enalapril and the latter captopril, and are aiming the intervention primarily at patients with low ejection fractions who are not necessarily symptomatic. Until these studies are completed, therapeutic interventions aimed at preventing progression of the syndrome must be viewed as experimental.

**Summary**

Myocardial dysfunction eventuating in systolic and diastolic pump function abnormalities is a consequence of a wide variety of cardiac diseases. The symptoms that develop in this syndrome appear to be related as much to peripheral and neurohormonal mechanisms as to the underlying pathological and cardiac functional abnormality. Relief of symptoms, slowing of the progression of the cardiac functional abnormality, and prolongation of life provide the major agenda for the physician faced with the management of these patients. Judicious use of vasodilators, diuretics, digoxin, dietary therapy, and exercise therapy can relieve symptoms and improve the quality of life in most patients suffering from this syndrome. Recent evidence that vasodilator drugs can prolong life now provides the physician with further justification for routine use of this class of compounds. The eventual solution to the high mortality in this common disease process may be prevention of the development of overt heart failure by more prompt recognition and early treatment of the signs of ventricular dysfunction. This possibility must await the completion of current and proposed clinical trials.

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| TABLE 1. Factors Possibly Contributing to Progression of Left Ventricular Dysfunction |
|-----------------------------------|----------------------------------|
| Increased ventricular wall stress | Myocardial hypertrophy           |
| Myosin isozyme change             | Collagen growth                  |
| Subendocardial ischemia           | Cellular calcium overload        |
| Catecholamine toxicity            | β-Receptor down-regulation       |
| Dyssynchronous contraction        | Right ventricular loading        |

*Note: This table lists factors that contribute to the progression of left ventricular dysfunction.*

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