Newer Drug Therapy for Congestive Heart Failure

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**Background:** The management of congestive heart failure has undergone a number of modifications over the past 5 to 10 years.

**Methods:** These include assaying the role of inotropic drugs, evaluating the role of phosphodiesterase inhibitors, considering the role of intermittent inotropic infusion in ambulatory patients, and recognizing the importance of angiotensin-converting enzyme inhibitors. Very recently, the important role of angiotensin II receptor blocking agents and the use of beta blockade have provided additional modalities for the control of congestive heart failure. The relative usefulness of such therapy has been reviewed in this article.

**Conclusion:** The management of congestive heart failure has undergone considerable change with the use of newer and more effective drugs.

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dose dependent. They studied a series of patients who were taking oral vesnarinone using either 30 mg/d or 60 mg/d for 3 months. The inotropic effect of vesnarinone was assessed by a recently validated index equal to the ratio of left ventricular maximum ventricular power divided by the square of end diastolic volume. It was felt that this ratio was sensitive to inotropic change but not altered by chamber loading. After 3 months of therapy at 60 mg/d, there was a 28% increase in the inotropic ratio together with a 21% increase in ejection fraction. These changes did not achieve statistical significance at the 30-mg/d dose. It was suggested that long-term treatment with vesnarinone modestly raises the inotropic state and lowers afterloads in patients with dilated cardiomyopathy, and these effects are dose dependent. Subsequent studies have indicated an increased mortality with the use of this agent.

Marius-Nunez and coworkers studied the effect of intermittent inotropic therapy in an outpatient setting for patients having refractory congestive heart failure. For 12 months, they observed 36 patients who were suffering from severe congestive heart failure. The patients received weekly inotropic infusions of milrinone or dobutamine. Thirty-two patients received milrinone and only 4 patients received dobutamine. The number of hospital admissions was markedly reduced with this regimen as were days spent in the hospital and emergency department visits. The authors suggested that intermittent inotropic therapy in an outpatient setting may play a major role in managing refractory congestive heart failure. Recommendation for intravenous inotropic support is coupled with the warning that most such agents are arrhythmogenic and result in increased myocardial oxygen demand.

In an earlier study, Applefeld and coworkers studied outpatient dobutamine therapy and dopamine infusions in the management of chronic congestive heart failure: the clinical experience in 21 patients was reported. Each patient was initially hospitalized, and the hemodynamic and clinical efficacy of dobutamine and dobutamine/dopamine combination was assessed. These 21 patients were carefully selected from a larger population of approximately 40 patients referred for this therapy. Chronic venous access was established and a drug infusion pump was supplied. Eleven patients were treated with intermittent dobutamine infusions for 48 consecutive hours weekly, 6 patients with continuous (ie, 24 hours daily) dobutamine infusions, and 4 patients with continuous daily dobutamine and dopamine infusions. Significant increases (P < .001) in the cardiac index (from mean ± SD, 1.8 ± 0.6 to 2.7 ± 0.7 L/min · m²) occurred during the initial dobutamine titrations. Functional classification also improved significantly (from 3.8 ± 0.4 to 2.8 ± 0.7 L/min · m²; P < .001) during the 1.8 to 24 months (mean, 7.8 months) of outpatient infusion therapy with dobutamine (and dobutamine/dopamine combination). Complications during outpatient therapy included drug tolerance (2 instances), infection (2 patients with bacteremias, 8 with exit-site infections), drug extravasation (3 instances), and pump malfunction (2 instances). Twenty patients died: 11 from congestive heart failure, 4 suddenly (1 of them 9 months after dobutamine treatment was stopped), and 5 from noncardiac causes. The data suggested that outpatient dobutamine and dobutamine/dopamine combination infusions may be an effective form of therapy for selected patients with severe congestive heart failure who are refractory to more conventional treatment.

Mori and associates reported on a comparison of the left ventricular mechanoenergetic effects on diseased hearts of a new Ca²⁺ sensitizing agent, MCI-154, and dobutamine. They found that left ventricular contractility was increased by both agents, but the oxygen cost of contractility was less with MCI-154 than with dobutamine. This was the result of altering the responsiveness of myofilament to Ca²⁺, generating force with smaller amounts of Ca²⁺ and thus saving energy expenditure. This class of drugs may have potential.

**CALCIAL CHANNEL BLOCKERS**

While calcium channel blockers have been found to increase mortality in patients with chronic congestive heart failure, a recent study was described by Packer and colleagues in which 1153 patients with severe chronic congestive heart failure were randomized to amlodipine maleate or placebo. These patients were observed for 6 to 33 months and the reduction of mortality in this study was 16%. Patients taking amlodipine were 9% less likely to suffer a fatal or nonfatal clinical event; this was primarily true of patients with nonischemic cardiomyopathy. In this latter group, amlodipine reduced the combined risk of fatal and nonfatal events by 31% and decreased mortality risk by 46%. All of the patients had severe chronic congestive heart failure with ejection fractions under 30%. Other calcium channel blockers have not proven beneficial in patients with congestive heart failure.

**ACE INHIBITORS**

When used in conjunction with diuretics and digoxin, ACE inhibitors have been shown to provide considerable benefit for patients with left ventricular systolic dysfunction. Borghi et al studied the effects of the early administration of xafenopril on the onset and progression of congestive heart failure in patients with acute myocardial infarction. This study involved 1146 patients with an anterior wall infarction not undergoing thrombolysis. Patients were randomized to xafenopril 7.5 to 30 mg twice daily or placebo for a period of 6 weeks. The prevalence of severe congestive heart failure and the combined occurrence of death or severe congestive heart failure were reduced after 6 weeks of treatment. The percentage of patients experiencing a deterioration to severe congestive heart failure after 1 year was significantly reduced with xafenopril (11% vs 24.3%; P = .001).

Khaper and Singal investigated the role of afterload-reducing drugs on changes in antioxidants and oxidative stress in relationship to home dynamic function in congestive heart failure. Postmyocardial congestive heart failure in rats is associated with a decrease in myocardial endogenous antioxidants and an increase in oxidative stress. This
study demonstrated for the first time that improved hemodynamic function subsequent to afterload reduction therapy in rats is associated with an increase in antioxidant levels and a corresponding decrease in oxidative stress. Khaper and Singal postulated that antioxidant deficit may play a role in the pathogenesis of postmyocardial congestive heart failure. The early use of ACE inhibitors should be regarded as a good strategy for the prevention and treatment of congestive heart failure in patients with acute myocardial infarction or marked left ventricular dysfunction.

β-BLOCKERS

Viskin and Barron have indicated that treatment with β-blockers improves the long-term prognosis of patients with myocardial infarction. Mortality and sudden death are reduced by 21% and 30%, and the risk of reinfarction is reduced by 25%. Impairment of left ventricular function and the use of diuretics are independent predictors of failure to prescribe β-blockers to infarct survivors. The presence of vascular disease in diabetes often leads to avoidance of β-blockers. The percentage of infarct survivors receiving β-blockers sharply declined from 65% among survivors with preserved left ventricular function to 30% among patients with ejection fractions below 30%. The rate of congestive heart failure precipitation requiring discontinuation of drug therapy among infarct survivors with a history of congestive heart failure was not more common among patients treated with β-blockers than among similar patients treated with placebo. In the Multicenter Post-Infarction Dilatation Trial, the incidence of congestive heart failure within 2 1/2 years after infarction among patients with poor left ventricular function was 46% for patients treated with β-blockers and 60% for patients not receiving such agents. It has been suggested that not recommending β-blocker treatment to patients with impaired left ventricular function may be depriving such patients of potential therapeutic gain. This fact is illustrated in the Norwegian Multicenter Study in which 2 lives were saved for each 100 patients with normal heart size treated with timolol maleate (compared with placebo), whereas among patients with cardiomegaly and impaired left ventricular function, the number of lives saved per 100 patients treated was 10. Although diabetes is frequently listed as a contraindication to the use of β-blockers, a study of more than 2000 patients indicated that the number of lives saved per 100 patients treated with β-blockers was 6 in patients without diabetes and 13 among those with diabetes. A study of survival among patients who were older than 70 years at the time of myocardial infarction indicated that these patients had the best prediction for survival if they were treated with β-blockers at the time of myocardial infarction.

Recent studies using β-adrenergic blocker therapy in chronic congestive heart failure have demonstrated improved left ventricular function, increased ejection fractions, and improved intrinsic systolic function. Carvedilol is a β-blocker-vasodilator that provides substantial improvement in left ventricular ejection fraction in subjects with both idiopathic dilated and ischemic cardiomyopathy. Quaife and coworkers studied the effects of carvedilol on diastolic and systolic left ventricular performance in both idiopathic dilated cardiomyopathy and ischemic cardiomyopathy. Thirty-six patients with New York Heart Association class II or class III symptoms or left ventricular ejection fractions below 35% were entered into either arm of a placebo-controlled, double-blind 4-month trial. Carvedilol therapy resulted in a substantial improvement of left ventricular fraction, from 0.22 to 0.30, when compared with the placebo group. No significant change in left ventricular diastolic function was noted. They concluded that this β-blocker had a marked positive effect on cardiac systolic performance but no measurable effect on diastolic left ventricular filling. However, 2 other studies of newer β-blockers have suggested that diastolic performance can likewise be improved. Such improvement was noted with the β-blocker vasodilator bucindolol and with the partial β-blocker xamoterol. The physiological benefit of β-blockers appears to be in slowing the heart rate, reducing arrhythmias, protecting microcytes from the toxic effects of catecholamine, up-regulating β-receptor density, restoring receptor coupling to the postreceptor pathway, and thus resulting in improvement in myocardial contractility and improved ejection fraction.

In an abstract presented in November 1996 at the American Heart Association meeting, Bristow and colleagues reported on 521 patients with ischemic heart disease and 570 patients with nonischemic heart disease, all with congestive heart failure and all treated with carvedilol. All-cause mortality was markedly reduced in both groups as compared with placebo, and global clinical assessment demonstrated reductions in the risk of worsening status and decreased hospitalization.

Eichhorn and Bristow analyzed the various β-blockers available and indicated that third-generation drugs such as bucindolol, labetalol, and carvedilol have the additional property of vasodilation as contrasted with first- and second-generation β-blockers. Carvedilol has antioxidant properties and bucindolol has minimal “inverse agonism” (the ability of a β-blocker to inactivate active-state receptors). Thus, agents with vasodilating properties and minimal inverse agonism are well tolerated and cause the least impairment of cardiac output. The third-generation β-blockers inhibit cardiac adrenergic stimulation better than first- or second-generation agents. Survival advantage for these third-generation agents will be evaluated by the ongoing Beta-Blocker Evaluation of Survival Trial and the Cardiac Insufficiency Bisoprolol Study II mortality trial.

Doughty and associates used quantitative 2-dimensional echocardiography to study the effect of carvedilol on left ventricular size and ejection fraction in patients with congestive heart failure. One hundred twenty-three patients were observed for 12 months and demonstrated reduced left ventricular...
The role of magnesium in congestive heart failure was studied by Douban and coworkers. They pointed out that the major intracellular cations, magnesium and potassium, may contribute to the high mortality and sudden death associated with congestive heart failure and that deficiency in these cations commonly occurs in congestive heart failure. Such deficiency may be the result of reduced intake secondary to decreased energy intake or may be associated with losses secondary to the drug therapy for congestive heart failure. They indicated that the largest study of hypomagnesemia in patients with congestive heart failure included 297 patients, 110 (37%) of whom demonstrated deficiency. The most common cause was the use of diuretic agents, particularly loop-blocking diuretic agents. It is also well recognized that the incidence of intracellular magnesium deficiency is higher than the serum magnesium level would suggest. Magnesium deficiency plays an important role in modifying risk factors of atherosclerosis. There is evidence that magnesium deficiency may contribute substantially to the development of cardiomyopathy as a result of endomyocardial fibrosis. The role of magnesium deficiency as an important cause of digitalis-toxic arrhythmia is well known. Magnesium deficiency plays a major role in congestive heart failure owing to its affecting risk factors for the development of congestive heart failure as well as complications of congestive heart failure, particularly arrhythmias. Magnesium therapy, both for deficiency replacement and in higher pharmacologic doses, has been beneficial in improving hemodynamics and in treating arrhythmias. Therefore, in patients with congestive heart failure, the presence of adequate total-body magnesium stores serves as an important prognostic indicator; low magnesium levels warrant replacement magnesium.

**DRUGS THAT SENSITIZE CARDIAC MYOFILAMENTS TO CALCIUM**

Despite optimal treatment with diuretics and ACE inhibitors, many patients with congestive heart failure continue to have persistent symptoms. The problems associated with inotropic stimulation have already been commented on. Long-term trials with phosphodiesterase inhibitors have been disappointing. A new approach to inotropic stimulation is the direct sensitization of cardiac myofilaments to cytosolic calcium. Investigators of pimobendan have studied the value of this drug in patients with congestive heart failure. This drug is thought to not only sensitize cardiac myofilaments to calcium but also inhibit myocardial adenosine monophosphate by curtailing phosphodiesterase inhibition. The drug is rapidly absorbed—peak plasma concentration is reached after 1.5 hours—and the effect lasts 8 to 10 hours. The major metabolite has similar pharmacodynamic properties. Several trials in chronic congestive heart failure showed beneficial effects when pimobendan was added to an optimal basic regimen. In the study by Katz et al, 317 patients with stable congestive heart failure and ejection fractions of 45% or lower who had been treated with diuretics and ACE inhibitors were observed with a test dose of pimobendan. Compared with placebo, pimobendan, both 2.5 and 5 mg daily, improved exercise duration by 6% after 24 weeks of therapy. Other studies have reported an increased mortality with these drugs.

**AMIODARONE**

Another drug used for the management of congestive heart failure is amiodarone, used primarily in the presence of ventricular tachycardia or ventricular fibrillation; Scheinman et al found that the frequency of arrhythmic events was reduced by 88% compared with baseline. This represents the first intravenous antiarrhythmic with all 4 Vaughan Williams class effects. It is primarily indicated for recurrent ventricular fibrillation or hemodynamically unstable ventricular tachycardia. Adverse effects include hypotension, bradycardia, liver function test abnormalities, and pulmonary fibrosis. In congestive heart failure aggravated or precipitated by recurrent arrhythmias, this agent has been found to be of considerable benefit. Although trials of amiodarone therapy in patients with congestive heart failure have produced discordant results with regard to effects on survival, most studies have reported a considerable rise in left ventricular ejection fractions during long-term therapy.

Massie and colleagues questioned whether this increase in ejection fractions was associated with an improvement in the symptoms and/or physical findings of congestive heart failure or a reduction in the number of hospitalizations for congestive heart failure. In their Department of Veterans Affairs cooperative study of amiodarone in congestive heart failure, 674 patients with Heart Association class II through class IV symptoms and ejection fractions of 40% or lower were treated with amiodarone or placebo for a median of 45 months.
in a randomized, double-blind, placebo-controlled protocol. Clinical assessments and radionuclide ejection fraction testing were performed at baseline and after 6, 12, and 24 months. Compared with the placebo group, ejection fractions increased more in the amiodarone group at each time point (8.1% ± 10.2% [mean ± SD] vs 2.6% ± 7.9% at 6 months; 8.0% ± 10.9% vs 2.7% ± 8.0% at 12 months; and 8.8% ± 10.1% vs 1.9% ± 9.4% after 24 months; P<.001 for all). However, this difference was not associated with greater clinical improvement, lesser diuretic requirements, or fewer hospitalizations for congestive heart failure (11.1% for amiodarone and 13.6% for placebo group; overall relative risk [RR] in the amiodarone group, 0.81 [95% confidence interval (CI), 0.56-1.10]; P = .18). Of note is the trend toward a reduction in the combined end point of hospitalizations and cardiac deaths (RR, 0.82 [95% CI, 0.65-1.03], P = .08), which was significant in patients with nonischemic etiology (RR, 0.56 [95% CI, 0.36-0.87], P = .01) and absent in the ischemic group (RR, 0.95). It was thought that although amiodarone therapy resulted in a substantial increase in left ventricular ejection fraction in patients with congestive heart failure, this was not associated with clinical benefit in the population as a whole. The substantial reduction in the combined end point of cardiac death plus hospitalizations for congestive heart failure in the nonischemic group suggested possible benefit in these patients.

Singh and coworkers42 studied amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmias (Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure). They indicated that symptomatic ventricular arrhythmias in patients with congestive heart failure are associated with increased rates of overall mortality and sudden death and that amiodarone is now used widely to prevent ventricular tachycardia and fibrillation. They used a double-blind, placebo-controlled protocol in which 674 patients with symptoms of congestive heart failure, cardiac enlargement, 10 or more premature ventricular contractions per hour, and left ventricular ejection fractions of 40% or less were randomly assigned to receive amiodarone (336 patients) or placebo (338 patients). The primary end point was overall mortality, and the median follow-up was 45 months (range, 0-54 months). There was no significant difference in overall mortality between the 2 treatment groups (P = .6). The 2-year actuarial survival rate was 69.4% (95% CI, 64.2%-74.6%) for the patients in the amiodarone group and 70.8% (95% CI, 65.7%-75.9%) for those in the placebo group. At 2 years, the rate of sudden death was 15% in the amiodarone group and 19% in the placebo group (P = .43). There was a trend toward a reduction in overall mortality among the patients with nonischemic cardiomyopathy who received amiodarone (P = .07). Amiodarone was significantly more effective in suppressing ventricular arrhythmias and increased left ventricular ejection fractions by 42% at 2 years. Although amiodarone was effective in suppressing ventricular arrhythmias and improving ventricular function, it did not reduce the incidence of sudden death or prolong survival among patients with congestive heart failure, except for a trend toward reduced mortality among those with nonischemic cardiomyopathy.

### ANTIALDOSTERONE THERAPY

Staessen and associates45 have described the rise in plasma concentration of aldosterone during long-term angiotensin II suppression. Aldosterone is known to be important in the pathophysiology of congestive heart failure. There is evidence that the currently recommended usual dosages of ACE inhibitors do not completely suppress aldosterone production.44 This escape of aldosterone despite ACE inhibition may be due, in part, to non-ACE-dependent angiotensin II production and to the fact that the control of aldosterone production may be independent of angiotensin II production via the action of atrial natriuretic factor. Staessen et al demonstrated that daily doses of 12.5 to 25 mg of spironolactone coadministered with conventional therapy of ACE inhibitors and loop diuretics were safe and effective in blocking the effects of aldosterone while at the same time reducing the potential for hypokalemia in patients with congestive heart failure.

### BRAIN NATRIURETIC HORMONE

A recent study45 has indicated that brain natriuretic hormone when injected intravenously produced substantial beneficial hemodynamic effects in patients with congestive heart failure and that the magnitude and duration of these changes were dose dependent. A study of 21 patients treated with drug and 6 with placebo showed a notable dose-dependent reduction of pulmonary capillary wedge pressure following administration of the brain natriuretic hormone. There was also a substantial decrease in pulmonary artery pressure, right atrial pressure, and mean arterial pressure. More importantly, there was an important dose-dependent effect of this drug on systemic vascular resistance together with a notable increase in cardiac index. This class of drugs, although still in an experimental phase, may afford important benefit in the management of congestive heart failure.

### ANGIOTENSIN RECEPTOR BLOCKADE

The introduction of an angiotensin II receptor blocking agent has encouraged studies in determining the value of these drugs in patients with left ventricular systolic dysfunction.46 Pitt and coworkers47 described the Randomized Angiotensin Receptor Antagonist-Angiotensin-Converting Enzyme Inhibitor Study, which employed angiotensin receptor antagonist as compared with placebo in patients with left ventricular systolic dysfunction and moderate to severe congestive heart failure. These patients were treated with standard therapy including ACE inhibitors. One hundred and twenty patients were randomized and observed for a 6-week period to determine the safety and tolerance and combination of losartan potassium and enalapril maleate. The rationale of this study depended on more complete blocking of the activation of the renin-
An algorithm for the diagnosis and management of heart failure in several stages, together with potential complications from drugs and their subsequent management. ACE indicates angiotensin-converting enzyme.

angiotensin aldosterone system in patients with congestive heart failure and left ventricular systolic dysfunction.

Kostis recently reviewed the pharmacologic action of angiotensin II receptor blockers. These drugs represent a new drug class for anti-hypertensive therapy but also have been used in the management of congestive heart failure. The renin-angiotensin system is involved in the pathophysiology of congestive heart failure. The primary active hormone of this system is angiotensin II, a powerful vasoconstrictive substance. Angiotensin II facilitates growth of the heart and blood vessels and has been associated with cardiac hypertrophy; it therefore has a role in the pathophysiology of congestive heart failure. While ACE inhibitors have been used effectively for a number of years in the management of congestive heart failure, it has been suggested that direct blockade of the angiotensin II receptor may afford additional benefit. The addition of the angiotensin II receptor blocking agent to an ACE inhibitor theoretically blocks ACE- as well as non-ACE-dependent angiotensin formation. This agent has been previously studied in patients with congestive heart failure. Dickstein and colleagues and Gottlieb et al studied the effect of losartan in congestive heart failure and demonstrated benefit.

The advantage of the angiotensin II receptor blockers is that they do not interfere with other hormonal systems or affect metabolic pathways. Angiotensin II has 2 receptor subtypes, type 1 (AT1) and type 2 (AT2). Pharmacological evidence indicates that most of the effects of angiotensin II are mediated by the AT1 receptor. An example of this class of drugs is losartan, which has been used in recent years for the management of hypertension. The drug can be administered orally, has no agonist activity, and has a long half-life that permits once-a-day dosing. The active metabolite is probably responsible for the long-term action of the drug. The hypertensive effect of losartan is similar to that of enalapril.

Abstracts from the American Heart Association annual meeting described combined ACE inhibition and angiotensin II receptor blockade in patients with congestive heart failure and found that the combination improved left ventricular pump function and myocyte capacity to respond to inotropic stimulus greater than monotherapy alone.

CONCLUSIONS

The management of congestive heart failure has undergone many phases of development, and newer drugs have a potential for facilitating more effective management of such failure (Figure). Common errors in management include the use of digoxin in diastolic congestive heart failure, high doses of negative inotropic agents such as β-blockers, failure INHIBITORS OF NEUTRAL ENDOPEPTIDASE

Cleland et al and Newby and co-workers described the beneficial effects of candesartan in patients with congestive heart failure. The mechanism is thought to be via inhibition of endopeptidase, a major clearance pathway for natriuretic peptides. More than 200 patients with New York Heart Association grade II or grade III chronic congestive heart failure were randomized in 2 separate studies with double blinding. A reduction in pulmonary capillary wedge pressure was noted both at rest and with exercise, and an improvement in exercise capacity was noted.

The role of diuretic therapy in congestive heart failure has been clearly defined and of course represents an initial modality in therapy. While furosemide is the most effective diuretic, the combination of several diuretic preparations may occasionally be required in patients with intractable congestive heart failure. The combination should include drugs acting at different sites in the kidney, ie, furosemide acts to block sodium resorption at the ascending loop of Henle, metolazone works at the distal tubule, aldactone works via sodium-potassium exchange, etc.

In selecting therapy for congestive heart failure, it is important to differentiate between systolic and diastolic forms of congestive heart failure. The former is characterized by a lowered ejection fraction, whereas the latter presents with a normal ejection fraction, frequently hypertension, an early-to-late ventricular filling ratio (E:A), and is most often found in older patients.