Recent Advances in the Treatment of Heart Failure

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Treatment strategies for patients with heart failure and left ventricular systolic dysfunction continue to evolve as the complex pathophysiology of this disease is better understood. A number of advances have been made in recent years, most notably the addition of receptor antagonists. In addition, recent studies have provided important information regarding the utility of angiotensin receptor antagonists, aldosterone receptor antagonists, and natriuretic peptides in the management of heart failure. Nonpharmacologic advances include resynchronization therapy, which appears to confer symptomatic improvement in some patients, and improvements in ventricular assist device technology. As the importance of neurohormonal activation in the progression of heart failure becomes increasingly apparent, new therapeutic strategies targeting these neurohormonal systems are being investigated. (Circ J 2002; 66: 117–121)

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Heart failure is a highly prevalent condition worldwide and remains a major cause of morbidity and hospitalization. Although there is evidence that survival has improved since the advent of angiotensin-converting enzyme (ACE) inhibitors as the standard therapy for heart failure, mortality rates remain high. In addition, this condition exacts a high economic cost because of the need for frequent and prolonged hospitalizations for decompensated heart failure. These challenges highlight the need for continued efforts to improve the morbidity and mortality associated with heart failure. A better understanding of the pathophysiology of this disease has led to a number of advances in the management of heart failure caused by ventricular systolic dysfunction.

ACE-Inhibitors and Angiotensin-Receptor Blockers

ACE-inhibitors remain the mainstay of therapy for patients with left ventricular systolic dysfunction. It is well-recognized that the renin-angiotensin–aldosterone system (RAAS) plays an important role in the progression of heart failure, promoting vasoconstriction and maladaptive ventricular remodeling. There is evidence that ACE-inhibition not only inhibits the RAAS, but also has bradykinin-related effects that may influence ventricular remodeling. The results of multiple large clinical trials support the use of ACE-inhibitors to improve survival in patients with heart failure.

More recently, angiotensin-II receptor blockers (ARBs) have emerged as an alternate agent for RAAS inhibition in patients who cannot tolerate ACE-inhibitors because of adverse effects, such as cough. Current ARBs selectively inhibit the angiotensin-II type 1 (AT1) receptor, which appears to mediate the deleterious effects of angiotensin-II in heart failure. The Evaluation of Losartan in the Elderly (ELITE) II trial was a randomized, prospective study designed to compare the effect of losartan versus captopril on mortality in patients who were at least 60 years old, had New York Heart Association (NYHA) Class II–IV symptoms, and a left ventricular ejection fraction (LVEF) of 40% or less. ELITE II failed to substantiate the hypothesis that losartan would reduce mortality compared with captopril; there was no significant difference in outcome between these 2 agents. Losartan was found to have a lower rate of withdrawal for adverse effects, particularly cough, compared with captopril. Nevertheless, given the large body of evidence supporting the beneficial effect of ACE-inhibition on clinical events, ACE-inhibitors remain the first-line agents for RAAS antagonism.

Because angiotensin may be produced by pathways independent of ACE, ARBs theoretically have the advantage of providing more complete antagonism of AT1-mediated effects, compared with ACE-inhibition alone. This observation raises the question of whether ARBs may have additional beneficial effects on outcome in patients who are already on background ACE-inhibitor therapy. The Valsartan Heart Failure Trial (Val-HeFT) was a large study designed to evaluate the effect of valsartan on outcomes in patients with NYHA Class II–IV heart failure and LVEF <40%, with the majority of patients receiving background ACE-inhibitor therapy. The primary end-point of the study was all-cause mortality and combined morbidity and mortality. Val-HeFT found no difference in mortality and a 13% decrease in the combined endpoint of morbidity and mortality in patients randomized to the valsartan treatment group. There was also a 27% reduction in heart failure hospitalizations in the valsartan group. However, most of the benefit of valsartan was observed in patients who were not on ACE-inhibitors or β-blocker therapy. Thus, the results of Val-HeFT provide evidence that ARBs are an effective alternative treatment in patients who are intolerant of ACE-inhibitor therapy. Another trial that is investigating the combined use of ARBs and ACE-inhibitors is the ongoing CHARM study, which is designed to evaluate the effect of candesartan on mortality and morbidity in patients with symptomatic heart failure.

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who are not on ACE-inhibitor therapy.

Beta-Receptor Antagonists

One of the major advances in recent years has been the addition of β-receptor antagonists as standard therapy for patients with heart failure of either ischemic or nonischemic etiology. Heightened adrenergic activity occurs in patients with heart failure, and increased levels of catecholamines have a variety of effects that can contribute to the progression of heart failure and promote arrhythmias. Carvedilol, a nonselective β-blocker with α-receptor blocker and antioxidant properties, has been extensively studied in this population. In the US Carvedilol study, treatment with carvedilol was associated with a 65% reduction in risk of death as well as a 27% decrease in cardiovascular hospitalizations in patients with LVEF ≤35% and mild–moderate heart failure. Similarly, the Cardiac Insufficiency Bisoprolol Study (CIBIS) II observed a 34% decrease in all-cause mortality, 32% decrease in hospitalizations for heart failure, and a reduction in sudden death in NYHA class III–IV patients who were treated with bisoprolol, compared with placebo. Although the study included some patients with NYHA Class IV heart failure, the majority of study subjects (83%) had Class III symptoms. More recently, the results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study, which examined the effect of carvedilol in patients with LVEF ≤25% and severe chronic heart failure, were reported. This trial demonstrated a 35% reduction in mortality and a 24% decrease in the combined endpoint of death or hospitalization in the treatment group, compared with placebo. Although it should be noted that patients with acutely decompensated heart failure were not included in the study, the majority of patients in the treatment group tolerated carvedilol (14.8% withdrawal rate vs 18.5% in the placebo group).

In addition, the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) demonstrated the tolerability and beneficial effect of long-acting metoprolol in patients with mild–moderate heart failure. In that study, patients treated with metoprolol had a 34% reduction in total mortality, 31% decrease in death or hospitalization for heart failure, and a 41% reduction in sudden death compared with placebo. Whether different β-receptor antagonists have a similar magnitude of effect remains unknown at this point, and it is hoped that the results of comparative studies, such as the Carvedilol or Metoprolol European Trial (COMET), will help elucidate this issue.

The use of β-blockade in patients with asymptomatic left ventricular dysfunction has not been as extensively studied. The Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial examined the effect of carvedilol in patients with recent myocardial infarction and left ventricular dysfunction (LVEF ≤40%), who were on ACE-inhibitor therapy. Approximately one-third of the patients required intravenous diuretics during the acute phase of their myocardial infarction. Patients were excluded if they continued to require intravenous diuretics or inotropes, or if they had uncontrolled heart failure. The initial primary endpoint was all-cause mortality, but during the course of the trial, the primary endpoint was split into all-cause mortality and the combination of mortality or cardiovascular hospitalizations (with a combined β=0.05). Mortality was lower in the carvedilol group compared with placebo, although not at the newly-specified p value, and the combined endpoint of mortality and cardiovascular hospitalizations was not significantly different between the 2 groups.

The use of β-blockade in asymptomatic nonischemic cardiomyopathy has not been examined in a large clinical trial. However, the benefit observed in patients with ischemic heart disease as well as those with symptomatic heart failure suggests that such therapy is likely to confer benefit in patients with asymptomatic dilated cardiomyopathy.

Aldosterone-Receptor Antagonists

The role of aldosterone in the pathophysiology of heart failure has led to recent investigation of the use of aldosterone receptor antagonists in the treatment of heart failure. Aldosterone’s myriad effects include promotion of sodium retention, myocardial and vascular fibrosis, increased sympathetic activity and decreased parasympathetic activity. Although ACE-inhibition can reduce aldosterone levels, there is evidence that the reduction is transient and that there are angiotensin-independent mechanisms for aldosterone production. The Randomized Aldactone Evaluation Study (RALES) evaluated the effect of spironolactone on survival in patients with left ventricular systolic dysfunction (LVEF ≤35%) and current or recent NYHA Class IV heart failure. Inclusion criteria for the trial included treatment with loop diuretics and ACE-inhibitors (unless intolerant). Most subjects were also treated with digoxin, but only a small percentage received β-blocker therapy. The spironolactone treatment group had a 30% reduction in risk of death, as well as decreased NYHA class and hospitalizations for heart failure compared with the placebo group. Although serious hyperkalemia was infrequent in the spironolactone group, it should be noted that patients were excluded if they had significant renal dysfunction (serum creatinine >2.5 mg/dl) or serum potassium greater than 5 mmol/L at baseline. Based on the findings observed in RALES, spironolactone appears to have a beneficial effect on survival and morbidity in patients with severe heart failure who are already on ACE-inhibitor therapy.

Natriuretic Peptides

It has been observed that circulating levels of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are elevated in patients with heart failure. ANP is predominantly produced in the atria, and BNP is released primarily from the ventricle in response to hemodynamic overload and myocardial stretch. These peptides have arterial and venous vasodilatory effects, as well as natriuretic effects and suppressive actions on the RAAS and sympathetic nervous system. In addition, there is evidence that ANP and BNP levels are predictive of prognosis. Recent studies have indicated that BNP may be superior to ANP or norepinephrine in predicting ventricular function and prognosis. Troughton et al recently examined the utility of aminoterminal BNP (N-BNP) as a tool to guide therapy in patients with NYHA Class II–IV heart failure. Sixty-nine patients were randomized to therapy guided by N-BNP levels versus therapy guided by standardized clinical assessment. Patients who underwent the N-BNP guided therapy had fewer cardiovascular events compared with the clinically-guided treatment group. Although the utility of BNP...
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The favorable hemodynamic effects of natriuretic peptides have generated interest in their use as therapeutic agents. A recombinant human BNP, nesiritide, has emerged as a new agent for the treatment of acutely decompensated heart failure. The Nesiritide Study Group reported the effect of nesiritide in an efficacy trial, which enrolled 127 patients who were hospitalized for acutely decompensated heart failure. The primary endpoint of the efficacy trial was a change in pulmonary capillary wedge pressure after 6 h of therapy. Treatment with nesiritide resulted in a decrease in pulmonary capillary wedge pressure and increase in cardiac index compared with placebo. A concomitant comparative trial, enrolling 305 patients, randomized subjects to nesiritide or one standard open-label intravenous vasoactive agent (predominantly dobutamine, milrinone, or nitroglycerin). The primary endpoints were global clinical status and clinical symptoms, and the degree of improvement in these parameters in nesiritide-treated patients was similar to that of the standard therapy group. The most common adverse effect in patients treated with nesiritide was hypotension, which occurred more frequently than in the standard therapy group.

The Vasodilator in the Management of Acute Congestive Heart Failure (VMAC) trial compared the hemodynamic and clinical effects of nesiritide with nitroglycerin in patients with acutely decompensated heart failure. The VMAC trial enrolled 498 patients, of whom 246 underwent invasive hemodynamic monitoring. Patients were allowed to continue standard heart failure therapy, including intravenous diuretics, dobutamine, and dopamine. The primary endpoints were pulmonary capillary wedge pressure and the patient’s dyspnea evaluation after 3 h of therapy. Nesiritide significantly lowered pulmonary capillary wedge pressure compared with placebo. The mean change in pulmonary capillary wedge pressure from baseline was \(-5.8\pm6.5\) for nesiritide (p<0.027 vs nitroglycerin, p<0.001 vs placebo), \(-3.8\pm5.3\) for nitroglycerin (p=NS vs placebo) and \(-2.0\pm4.2\) for placebo. It should be noted that, although the dosing of nitroglycerin was left to the investigator’s discretion, the mean dose of nitroglycerin was low. At 3 h, dyspnea had improved in patients treated with nesiritide, compared with placebo (p=0.034). The incidence of symptomatic hypotension was similar in the nesiritide and nitroglycerin groups (4% vs 5%, respectively). However, the mean duration of symptomatic hypotension was longer with nesiritide than with nitroglycerin (2.2 h vs 0.7 h). The overall incidence of adverse effects was lower in nesiritide-treated patients compared with the nitroglycerin treatment group, predominantly because of a lower incidence of headache with nesiritide.

Resynchronization Therapy

There is a high prevalence of intraventricular conduction delay in patients with heart failure, and the presence of a widened QRS appears to be associated with a worsened prognosis. Intraventricular conduction abnormalities may result in poor coordination of left and right ventricular contraction and aberrant ventricular relaxation, resulting in worsened hemodynamics. These observations have led to the investigation of left ventricular and biventricular pacing to achieve ventricular re-synchronization. The Multisite Stimulation in Cardiomyopathies (MUSTIC) trial was a prospective, controlled, cross-over study of the effect of biventricular pacing on symptoms in patients with NYHA Class III heart failure and a QRS interval of greater than 150 ms. This was a relatively small study (48 patients completing both phases) with a primary endpoint of a 6-min walk after 3 months of treatment. The 6-min walk distance was greater in the active pacing group compared with the inactive pacing group (399±100 m vs 326±134 m, p<0.001). Secondary endpoints of peak oxygen consumption and quality of life score were improved in the actively paced patients compared with the inactive pacemaker group, and heart failure hospitalizations were reduced in the active pacing group.

The largest biventricular pacing study thus far is the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial, a randomized, prospective, double-blinded study in patients with NYHA class III–IV heart failure, LVEF ≤35%, and QRS duration of at least 130 ms. The primary endpoint of the study was change in functional status at 6 months, as measured by NYHA class, 6-min walk distance, and quality of life questionnaire. Results from the first 244 patients to complete 6 months of follow-up demonstrated a significant improvement in NYHA class, 6-min walk distance, and quality of life score. Sixty-nine percent of patients in the active pacing group improved by at least 1 NYHA class, compared with 34% in the inactive pacing group (p<0.001). The device was successfully implanted in 93% of subjects. Although criteria for select-

Table 1  Targets for Neurohormonal Modulation in Heart Failure

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<tr>
<th>Drug</th>
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<tr>
<td><strong>Established therapies</strong></td>
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<tr>
<td>ACE-inhibition</td>
<td>Decreased angiotensin II levels, increased bradykinin levels (vasodilation, decreased sodium retention, effects on myocardial remodeling)</td>
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<tr>
<td>Angiotensin II receptor blockade</td>
<td>Blockade of angiotensin II (AT1-mediated) effects</td>
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<tr>
<td>Beta-blockade</td>
<td>Decreased adrenergic activity</td>
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<tr>
<td>Aldosterone receptor antagonism</td>
<td>Inhibition of aldosterone effects (decreased sodium retention, possible effects on myocardial fibrosis)</td>
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<td>Brain natriuretic peptide (acute therapy)</td>
<td>Arterial and venous vasodilation</td>
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<td><strong>Investigational therapies</strong></td>
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<tr>
<td>Vasopeptidase inhibition</td>
<td>a) ACE-inhibition</td>
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<tr>
<td>Vasopressin receptor antagonism</td>
<td>b) Neutral endopeptidase inhibition (increased natriuretic peptide and bradykinin levels)</td>
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<tr>
<td>Endothelin receptor antagonism</td>
<td>Vasodilation (V1a blockade); Free water excretion (V2 blockade)</td>
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<td>Inhibition of endothelin effects (decreased vasconstriction)</td>
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ing optimal candidates for this therapy have not been fully defined, these data indicate that biventricular pacing confers symptomatic improvement in some patients who have moderate to severe symptoms despite standard medical therapy.

**Ventricular Assist Devices**

Another nonpharmacologic advance in the treatment of severe heart failure is the improvement in ventricular assist device technology, and the growing use of these devices in patients with end-stage heart failure. Ventricular assist devices are currently used in clinical practice as a bridge to cardiac transplantation in patients with refractory heart failure. However, the use of ventricular assist devices and total artificial heart devices as destination therapy is being investigated, and may ultimately provide an alternative therapeutic option in patients with end-stage heart failure.22,23

**New Approaches**

Despite the advances that have been made in the treatment of heart failure, morbidity and mortality rates remain high, necessitating new therapeutic approaches as well as improved utilization of established therapies. It has become increasingly evident that a variety of interwoven neurohormonal derangements contribute to the progression of heart failure. Greater understanding of these processes is providing newer targets for potential intervention (Table 1). One area of investigation has been endothelin receptor antagonists, because circulating levels of endothelin (a potent vasoconstrictor) are elevated in patients with heart failure and correlate with prognosis. Recently, the Randomized Intravenous Tezosentan (RITZ)-2 study reported that tezosentan (a dual endothelin receptor A and B antagonist) improved hemodynamics in patients with acutely decompensated heart failure.24 However, tezosentan did not improve symptoms associated with acutely decompensated heart failure in the subsequently reported RITZ-1 study. In addition, the Enrasentan Cooperative Randomized (ENCOR) trial reported that enrasentan, another nonselective endothelin antagonist, was associated with worsened clinical outcome in patients with chronic heart failure.25 The ENABLE trial, a phase III investigation of the effect of bosentan on clinical status in patients with severe heart failure, is underway and will provide further information about the utility of dual endothelin receptor antagonists.

An additional class of agents under investigation are vasopeptidase inhibitors26 which have combined effects of ACE-inhibition as well as inhibition of neutral endopeptidase, an enzyme that degrades natriuretic peptides. The effects of the vasopeptidase inhibitor omapatrilat on clinical outcome are currently being evaluated in the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) study. There has also been growing interest in vasopressin receptor antagonists as potential therapeutic agents in heart failure. Vasopressin promotes vasoconstriction through vascular (V1a) receptors, and enhances water retention via renal tubular (V2) receptors. Initial clinical studies of the effect of vasopressin dual receptor antagonists and selective V2 receptor antagonists on fluid balance appear promising.27,28 and additional clinical trials are underway to further evaluate their efficacy. Although these newer classes of agents will require further investigation to determine their effect on clinical outcome, they may ultimately provide novel approaches for the treatment of heart failure.

**References**


