

Pharmacologic Treatment of Chronic Systolic Heart Failure: Past, Present, and Future

Ishak A. Mansi, MD; Jian Huang, MD; Donna Carden, MD

ABSTRACT

PURPOSE: To review the pharmacologic management of chronic systolic heart failure (HF).

EPIDEMIOLOGY: Approximately 550 000 new cases of HF are diagnosed each year with a mortality rate of 20.1 per 100 000 population.

REVIEW SUMMARY: Early clinical trials in HF focused on the use of inotropic and antiarrhythmic agents for the most common modes of mortality in chronic systolic HF: progressive pump failure and sudden cardiac death. The fact that these agents not only failed to improve survival but actually increased mortality led to an improved understanding of the neurohormonal compensatory mechanisms operative in HF. This, in turn, led to the current concept that interrupting these compensatory mechanisms improves outcomes in chronic HF.

TYPE OF AVAILABLE EVIDENCE: Unstructured review, randomized-controlled clinical trials, cohort studies, case series.

GRADE OF AVAILABLE EVIDENCE: Good.

CONCLUSION: Early clinical HF trials aimed at reducing direct modes of mortality in HF. Presently, HF trials are chiefly focused on antagonizing the neurohormonal compensatory mechanisms activated in this disorder. Future therapeutic interventions may be directed at strategies to avoid activation of the neurohormonal system altogether.

(*Adv Stud Med.* 2005;5(2):81-89)

Hear failure (HF) is the final, common pathway in most heart diseases. Approximately 550 000 new cases of HF are diagnosed each year with a mortality rate of 20.1 per 100 000 individuals. Despite significant advances in the diagnosis and treatment of HF, the overall mortality rate associated with this disorder has not changed.¹

Traditionally, HF has been thought of as failure of the systolic, or pumping, function of the heart. Recently, it has been recognized that HF also may occur in the presence of preserved systolic function, occasionally called diastolic dys-

function. Although such hearts contract normally, their ability to accept blood and relax during diastole is impaired. The prevalence of both types of HF increases with age and is particularly high among African Americans, in whom the disease appears to have an accelerated course.² The proportion of patients with diastolic HF ranges from 40% to 70%³ and these patients are more often female, obese, older (mean age, 60 to 78 years), more likely to have hypertension, and less likely to have coronary artery disease than patients with systolic HF.³ Patients with diastolic HF also tend to be less symptomatic and have lower morbidity and mortality rates than those

Dr Mansi is Clinical Associate Professor of Medicine; Dr Huang is Assistant Professor of Medicine; and Dr Carden is Professor of Medicine and Emergency Medicine, Louisiana State University Health Sciences Center, Department of Medicine, School of Medicine in Shreveport, La.

Conflict of Interest: Drs Mansi, Huang, and Carden report having no financial or advisory relationships with corporate organizations related to this activity.

Off-Label Product Discussion: The authors of this article do not discuss off-label use of products.

Correspondence to: Donna Carden, MD, Professor of Medicine and Emergency Medicine, Louisiana State University Health Science Center, School of Medicine in Shreveport, 1501 Kings Highway, Shreveport, LA 71130.

with systolic failure.³ Few clinical trials have addressed the pharmacologic treatment of diastolic HF and results from trials of systolic HF cannot be extrapolated to patients with preserved systolic function. Thus, the remainder of this review focuses on the pharmacologic treatment of chronic systolic HF.

Current treatment of systolic HF includes pharmacologic, dietary, electrical (via cardiac resynchronization and defibrillators), and surgical intervention, as well as cardiac rehabilitation. The pharmacologic approach to treatment of systolic HF has changed during the past several decades as our understanding of the mechanisms responsible for the disorder has evolved.

NATURAL HISTORY OF HEART FAILURE

Epidemiologic studies indicate that the high mortality rate in systolic HF patients⁴ occurs not only through progressive pump failure, but also sudden cardiac death.⁵ In fact, 30% to 50% of HF patients die of sudden cardiac death,⁵ presumably due to ventricular arrhythmias. Accordingly, pharmacologic interventions in the late 1980s and throughout the 1990s were directed at the 2 most common modes of mortality in chronic systolic HF: progressive pump failure and sudden cardiac death.

PAST: TREATMENT INTERVENTIONS FOR HEART FAILURE

It was assumed that since patients with HF die of progressive pump failure, inotropic medications should improve survival. Numerous inotropic agents were known to be effective at improving cardiac func-

tion in acute HF, however, the efficacy of these did not translate to a similar degree of success in chronic HF. Table 1 summarizes the results of some of these trials, which clearly demonstrated that all inotropic agents, regardless of mechanism of action, increased mortality⁶⁻¹¹ with the exception of digoxin, which neither increased nor decreased mortality.¹²

The fact that patients with chronic HF often died of sudden cardiac death led to the assumption that antiarrhythmics also should improve survival in HF. The efficacy and tolerability of the Vaughan-Williams class IC antiarrhythmic medications (encainide, flecainide, and moricizine) were demonstrated in the Cardiac Arrhythmia Pilot Study (CAPS).¹³ Based on the results of the CAPS study, the Cardiac Arrhythmia Suppression Trial (CAST) was undertaken to evaluate the effects of encainide, flecainide, and moricizine in patients who had suffered acute myocardial infarction (MI), and had an ejection fraction of less than 40% and asymptomatic ventricular arrhythmias. In April 1989, the CAST study was prematurely terminated due to a 2- to 3-fold increase in mortality in the encainide and flecainide arms, compared with placebo.¹⁴ The moricizine arm was later terminated, as well.¹⁵ The findings of the CAST study were consistently repeated in studies of other antiarrhythmics. The Survival With Oral D-sotalol study (SWORD) showed that d-sotalol increased mortality in patients with left ventricular dysfunction.¹⁶ Trials of amiodarone in patients with HF after MI,^{17,18} as well as a subsequent meta-analysis,¹⁹ suggest that amiodarone is either neutral or has a modest survival benefit.

INSIGHTS INTO THE PATHOPHYSIOLOGY OF HEART FAILURE

Figure 1 illustrates some of the neurohormonal compensatory mechanisms activated in chronic HF. These include increased sympathetic nervous system activity, increased renin-angiotensin-aldosterone system (RAAS) activity, and increased production of arginine-vasopressin (AVP), endothelin, and natriuretic peptides.

In the heart, increased sympathetic activity may lead to desensitization of postsynaptic β -receptors, heterogeneous depletion of norepinephrine stores and destruction of sympathetic nerve terminals, arrhythmias, and impairment of diastolic function. Enhanced sympathetic stimulation also may directly injure the myocyte, causing hypertrophy, necrosis, apoptosis, and fibrosis.²⁰ In the kidneys, increased sympathetic activation causes vasoconstriction, activation of the RAAS, and diminished response to natriuretic factors. In peripheral vessels, increased sympathetic activation may cause vasoconstriction and vascular hypertrophy.²⁰

Table 1. Effect of Inotropic Agents on Mortality in Heart Failure

Drug	Mechanism of Action	Study	Mortality
Dobutamine	β -adrenergic receptor agonist	FIRST ⁶	Increased
Ibopamine (oral dopamine analog)	Adrenergic receptor agonist	PRIME II ⁷	Increased
Xamoterol	β_1 -selective partial adrenergic agonist	Xamoterol ⁸	Increased
Milrinone	Phosphodiesterase III inhibitor	PROMISE ⁹	Increased
Vesnarinone	Phosphodiesterase III inhibitor + potassium channel antagonism	VEST ¹⁰	Increased
Pimobendan	Phosphodiesterase III inhibitor + calcium sensitizer	PICO ¹¹	Increased
Digoxin	Na ⁺ -K ⁺ -ATPase inhibitor	DIG ¹²	No effect

FIRST = Flolan International Randomized Survival Trial; PRIME II = second Prospective Randomised Study of Ibopamine on Mortality and Efficacy; PROMISE = Prospective Randomized Milrinone Survival Evaluation Trial; VEST = Vesnarinone Trial; PICO = Pimobendan in Congestive Heart Failure trial; DIG = The Digitalis Investigation Group.

Activation of the RAAS in HF results in local and systemic elevations of angiotensin II. The effects of angiotensin II on the heart include increased inotropy, impaired diastolic function, left ventricular remodeling, and coronary vasoconstriction. Effects on blood vessels include decreased compliance, increased resistance, and structural remodeling.²¹

The serum level of AVP, a peptide synthesized by the hypothalamus, is elevated in HF.²² Vasopressin elicits vasoconstriction via vasopressin-1 receptors, and induces renal reabsorption of water and secretion of renin. The natriuretic peptide (NP) family includes atrial-NP, brain-NP, C-type NP, and urodilatin. Atrial-NP and brain-NP increase urine volume and sodium excretion, decrease vascular resistance, and inhibit renin release and secretion of aldosterone and vasopressin.²³

Endothelin is a potent endogenous vasoconstrictor peptide produced by endothelial cells. Angiotensin II, vasopressin, and epinephrine stimulate release of endothelin. Endothelin in turn increases circulating atrial natriuretic factor, vasopressin, and aldosterone. Endothelin has a positive inotropic effect and produces coronary and systemic vasoconstriction.²⁴

EFFECTS OF INOTROPIC AGENTS AND ANTIARRHYTHMICS ON THE PATHOPHYSIOLOGY OF HEART FAILURE

Neurohormonal stimulation contributes to progressive left ventricular remodeling, progressive pump failure, and lethal arrhythmias. The remodeling process includes dilatation, altered left ventricular geometry (rendering it more spherical), hypertrophy, loss of myocytes, and increased interstitial fibrosis.^{25,26}

Inotropic therapy may cause increased mortality in HF via a number of mechanisms. Catecholamines may exacerbate underlying ischemia or induce malignant ventricular arrhythmias.²⁷ Long-term adrenergic stimulation may have a direct toxic effect on the myocardium.²⁷ Inotropic agents that inhibit phosphodiesterase III also appear to precipitate arrhythmias and lead to progression of HF when taken frequently. Stimulation of contractility in the hibernating myocardium, without restoration of blood flow, appears to increase short-term contractility at the expense of accelerating apoptosis and further degeneration of myocardial function.²⁷

There also is significant heterogeneity in the electrical properties of myocytes in HF in response to ischemia, inflammation, fibrosis, and apoptosis, as shown in Figure 1. This heterogeneity enhances the susceptibility of the myocardium to arrhythmias. Moreover, the myocardial conduction system is vulnerable to these same pathophysiologic processes. Ventricular arrhythmias are thought to be secondary to a dispersion of normal conduction through nonho-

mogenous myocardial tissue, which promotes repetitive ventricular and supraventricular arrhythmias.²⁸ Antiarrhythmics may increase the electrical heterogeneity of myocytes and the conduction system, thereby aggravating arrhythmias.

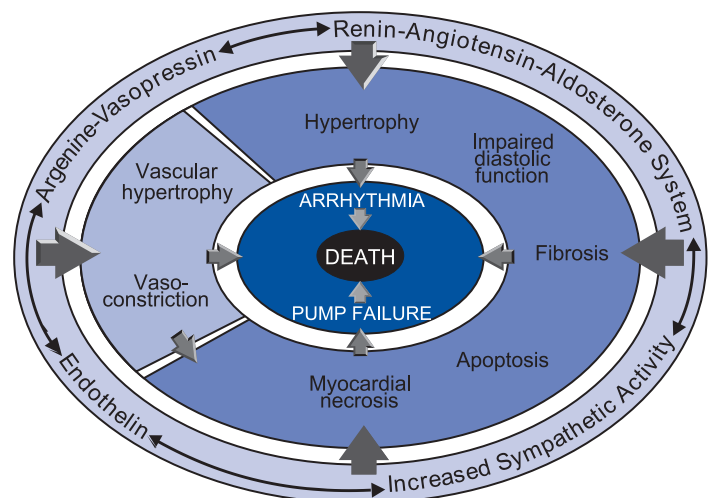
PRESENT: STANDARD PHARMACOLOGIC TREATMENT OF HEART FAILURE

Currently, the pharmacologic treatment of HF is directed at blocking the neurohormonal compensatory mechanisms outlined above. Figure 2 shows that medications that block the RAAS or sympathetic nervous system activation improve survival in HF. These include angiotensin-converting enzyme inhibitors (ACE inhibitors), β -adrenergic receptor blocking agents (β -blockers), angiotensin receptor blockers (ARBs), aldosterone antagonists, and selective blockers (Table 2).

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

ACE inhibitors decrease the conversion of angiotensin I to angiotensin II and decrease the degradation of bradykinins. The ability of ACE inhibitors to modify the natural history of HF has been demonstrated by studies that showed ACE inhibitors to improve survival, decrease rate of hospitalization, improve symptoms, inhibit neurohormonal activation, and reverse cardiac remodeling in HF.^{29-33,43,44} ACE inhibitors should be prescribed to all patients with systolic HF unless there is a specific contraindication to their use.⁴⁵ Although ACE inhibitors are devoid of intrinsic antiarrhythmic properties, they have been

Figure 1. Neurohormonal Compensatory Mechanisms in Heart Failure



shown in some studies to decrease the incidence of sudden death in HF patients,⁴⁶ confirming the effectiveness of neurohormonal blockade in decreasing the endpoints of both progressive pump failure and sudden arrhythmic death. ACE inhibitors are generally well tolerated; side effects, including hypotension, hyperkalemia, renal insufficiency, cough, angioneurotic edema, and anaphylactoid reactions, are few.

β-ADRENERGIC RECEPTOR BLOCKERS

Historically, β-blockers were contraindicated in HF.⁴⁷ Currently, β-blockers have been evaluated in more than 10 000 patients with various grades of HF in more than 20 placebo-controlled clinical trials. The effects of β-blockers include improved survival, ejection fraction, remodeling, quality of life, and rate of hospitalization, and reduced incidence of sudden death.^{34,48,49} β-blockers act principally by inhibiting the

adverse effects of the sympathetic nervous system in patients with HF. Whereas cardiac adrenergic drive supports the performance of the failing heart, long-term activation of the sympathetic nervous system exerts deleterious effects that can be antagonized by the use of β-blockers. β-blockers also block sympathetic-nervous-system-elicited renin secretion, thereby diminishing RAAS activation.⁵⁰ β-blockers are thus first-line therapy for stable HF patients who can tolerate them.⁴⁵

ANGIOTENSIN RECEPTOR BLOCKERS

Several clinical trials have shown that ARBs have efficacy similar to that of ACE inhibitors regarding morbidity and mortality in HF.^{51,52} The American College of Cardiology (ACC) and American Heart Association (AHA) guidelines for management of chronic HF in 2001 recommended the use of ARBs as an alternative in patients who do not tolerate ACE inhibitors.⁴⁵ The use of ARBs as first-line treatment with ACE inhibitors also has been the subject of recent clinical trials. In the subgroup analysis of the Valsartan in Heart Failure Trial (VAL-HeFT), addition of valsartan (an ARB) in patients taking both an ACE inhibitor and β-blocker was associated with increased mortality.³⁶ In the Valsartan In Acute Myocardial Infarction Trial (VALLIANT), combining valsartan and the ACE inhibitor captopril in patients with MI complicated by low ejection fraction increased the rate of adverse events without improving survival.³⁷ However, the Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity (CHARM) study recently evaluated the addition of the ARB candesartan in HF patients taking both an ACE inhibitor and a β-blocker. Adding candesartan resulted in a significant reduction in HF morbidity and mortality.³⁸

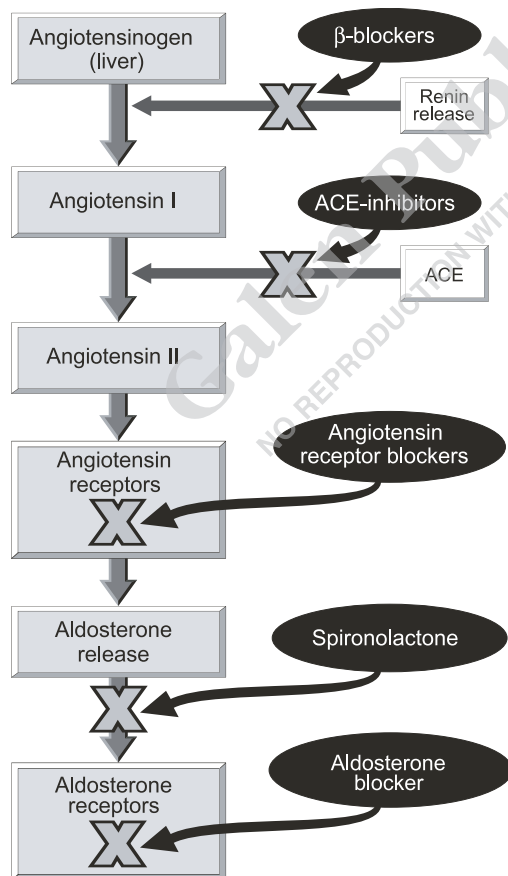
COMPETITIVE ALDOSTERONE ANTAGONISTS

Aldosterone stimulates renal sodium retention, potassium excretion, and myocardial hypertrophy. Spironolactone, a competitive aldosterone antagonist, has been shown to reduce morbidity and mortality in patients diagnosed with New York Heart Association (NYHA) class III and IV HF.³⁹

SELECTIVE ALDOSTERONE BLOCKERS

The effects of eplerenone, a selective aldosterone blocker, were evaluated in the Eplerenone Post Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS). The addition of eplerenone to optimal medical therapy, including ACE inhibitors and β-blockers but excluding spironolactone, reduced morbidity and mortality in patients with acute MI complicated by left ventricular dysfunction and HF.⁴⁰

Figure 2. Pharmacologic Blockade of the Renin-Angiotensin-Aldosterone System



ACE = angiotensin-converting enzyme.

HYDRALAZINE AND ISOSORBIDE DINITRATE

In a large-scale placebo-controlled trial, combined treatment with hydralazine and isosorbide dinitrate reduced mortality but not hospitalization rates in HF patients treated with digoxin and diuretics but not with ACE inhibitors or β -blockers.⁴¹ Different theoretical and experimental explanations were suggested for their effect and are beyond the scope of this article.⁴⁵ Currently, this combination may be considered for patients who cannot tolerate ACE inhibitors or ARBs.⁴⁵

Although results of clinical trials of medications that interfere with neurohormonal activation in HF have been promising, not all trials with these agents have consistently resulted in improved survival. Table 3 shows various neurohormonal blockers that failed to improve or worsened survival.⁵³⁻⁶⁰ Some investigators believe there is a limit to what can be achieved through interference with the neurohormonal cascade.⁶¹ Although persistent activation of the RAAS and the sympathetic nervous system results in adverse hemodynamic abnormalities and progressive HF, neurohormonal compensatory mechanisms are activated to maintain homeostasis in the face of diminished cardiac output and may be life saving in acute HF.^{62,63} Thus, it is not surprising that abolishing neurohormonal activation completely may be detrimental. Alternatively, it is possible that the HF patient who requires multiple blocking drugs is more severely ill and consequently more likely to have a worse outcome than patients who respond to a single agent.

RECLASSIFICATION OF HEART FAILURE

The ACC/AHA introduced a new classification for HF in 2001 that emphasized the evolution and progression of HF through 4 stages (Table 4).⁴⁵ Stage A includes patients at high risk for HF but without apparent structural abnormality, whereas stage D includes patients with end-stage symptoms of HF refractory to standard treatment. Previous HF classifications, including the NYHA classification, depended on the functional status of patients. This scheme delayed classifying HF patients until neurohormonal compensations and myocardial damage were

Table 2. Current Pharmacologic Therapy for Chronic Systolic Heart Failure

Class of Medication	Trial Name	Effect
ACE-inhibitors (enalapril, ramipril, captopril, trandolapril)	CONSENSUS, ²⁹ SOLVD, ³⁰ SAVE, ³¹ AIRE, ³² TRACE ³³	Reduced morbidity and mortality
β -blockers (carvedilol, metoprolol CR/XL, bisoprolol)	MERIT-HF, ³⁴ Carvedilol US ³⁵	Reduced morbidity and mortality
Angiotensin receptor blocker (valsartan, candesartan)	VAL-HeFT, ³⁶ VALLIANT, ³⁷ CHARM ³⁸	Reduced morbidity and mortality
Aldosterone antagonist (spironolactone)	RALES ³⁹	Reduced morbidity and mortality
Selective aldosterone blockers (eplerenone)	EPHESUS ⁴⁰	Reduced morbidity and mortality
Hydralazine + isosorbide (dinitrate)	V-HeFT ⁴¹	Reduced mortality
Diuretics	Cody RJ ⁴²	Improved symptoms
Digoxin	DIG ⁴²	Improved morbidity but not mortality

ACE = angiotensin-converting enzyme; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; SOLVD = Studies of Left Ventricular Dysfunction; SAVE = Survival and Ventricular Enlargement trial; AIRE = Acute Infarction Ramipril Efficacy; TRACE = Trandolapril Cardiac Evaluation; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; VAL-HeFT = Valsartan in Heart Failure Trial; VALLIANT = Valsartan In Acute Myocardial Infarction; CHARM = Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity; RALES = Randomized Aldactone Evaluation Study; EPHESUS = Eplerenone Post Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; V-HeFT = Veteran’s Administration Heart Failure Trial; DIG = The Digitalis Investigation Group.

Table 3. Neurohormonal Blocking Trials That Failed to Show Improved Survival

Mechanism of Action	Drug	Study	Effect
Excessive sympatholysis: – Central acting sympatholytic	Moxonidine	MOXSE, ⁵⁴ MOXCON, ⁵⁹ BEST ⁵⁵	Increased mortality*
– “Strong” β -blocker	Bucindolol		No benefit on mortality [†]
Endothelin antagonist	Bosentan	ENABLE ⁵⁶	No benefit on all-cause mortality or hospitalization
Vasopeptide inhibitor	Omapatrilat	OVERTURE ⁵³	No survival benefit
TNF- α	Etanercept	RENNAISSANCE ^{57,58} RENEWAL ⁵⁸	Premature termination Trend toward worsening

MOXSE = Moxonidine Safety and Efficacy; MOXCON = Moxonidine Congestive Heart Failure; BEST = Beta-blocker Evaluation of Survival Trial; ENABLE = Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure; OVERTURE = Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events; RENNAISSANCE = Randomized Etanercept North American Strategy to Study Antagonism of Cytokines; RENEWAL = combined analysis of the RENNAISSANCE and RECOVER trials; TNF = tumor necrosis factor.

*Plasma norepinephrine was markedly reduced, with evidence of reverse remodeling, but with increased adverse events.

[†]Profound sympatholysis was linked to excess mortality.⁶⁰

evident. By contrast, defining a stage of HF in which no structural, functional, or symptomatic abnormality exists (eg, ACC/AHA guidelines) has important implications in that it underscores the need to recognize and treat patients at high risk for HF before progressive myocardial damage occurs. As of this writing, updated guidelines for the classification of HF from the ACC/AHA are anticipated.

FUTURE: NEW INSIGHTS INTO THE TREATMENT OF HEART FAILURE

The future treatment of HF may be directed at preventing neurohormonal compensatory mechanisms before hemodynamic alterations and cardiac and vascular remodeling occur.^{28,61}

IMPROVED IMAGING TECHNIQUES

According to the current ACC/AHA classification of HF, stage A HF includes patients with hypertension, ischemic heart disease, diabetes mellitus, history of cardiotoxic drug therapy or alcohol abuse, or family history of cardiomyopathy. Stage A patients represent a heterogeneous population with variable natural histories. The absence of structural or functional abnormalities on current imaging techniques may reflect the insensitivity of these techniques. New imaging technology may be more sensitive to subtle structural or functional changes and may be used to define patients whose HF is likely to progress. Recent studies using tissue Doppler imaging have suggested that decreased flow velocities are predictive of the development of hypertrophic cardiomyopathy before hypertrophy actually develops.⁶⁴ Reduced myocardial function by tissue Doppler imaging also has been demonstrated prior to development of hypertrophy in Fabry's disease, among patients with normal ejection fraction.⁶⁴

Ultrasonic tissue characterization has been used successfully to assess alterations in tissue edema, fibrosis, and calcification.⁶⁵ Ultrasonic tissue characterization is based on quantitation of signals arising within the myocardium and is closely correlated with tissue collagen content. Moreover, cyclic variation of these signals correlates with left ventricular mass in patients with essential hypertension, and predicts changes in function before changes in fractional shortening are evident.⁶⁶ Magnetic resonance spectroscopy also has been used to detect creatine depletion associated with the progression of HF in cardiomyopathy.⁶⁷

Such advances in imaging may allow subclassification of early stages of HF, which in turn may inform specific treatment recommendations for this diverse group of patients.

PHARMACOGENETICS

Advances in genetics and genomics may allow for better characterization of HF and facilitate gene-informed therapy.^{68,69} Such an approach would allow physicians to determine the genetic risk of patients and to determine effective intervention based on genetic profiling. Several examples illustrate this possibility. Psaty et al reported that in two thirds of hypertensive patients with the α -adducin gene, diuretic treatment does not reduce the risk of MI or stroke.⁷⁰ Similarly, Small et al described 2 synergetic variants for adrenergic receptors.⁷¹ African Americans with both of these gene variants have a greater than 10-fold risk of developing hypertension, making these patients candidates for very early therapy with an α_2 -agonist or β -blockers.

Recently, myocyte enhancer factor 2, a developmental gene, was found to be critical to coronary artery development, and is strongly linked to MI⁷² or nonischemic HF.⁷³ The presence of specific variants of genes for connexin 37 (resulting in changes in endothelial gap junctions) in men and in genes for plasminogen activator inhibitor-1 and stormelysin-1 (associated with altered matrix metabolism) in women are associated with increased risk of MI.⁷⁴ Genetic polymorphism in the RAAS has been linked to response to ACE inhibitors⁶⁹ or spironolactone,⁷⁵ and to progression and prognosis of HF.⁶⁹ Genetic polymorphisms of the adrenergic system and aldosterone synthase also have been reported to affect the progression of HF, response to medications, or propensity to side effects.⁶⁹

TARGETING APOPTOSIS

Apoptosis is programmed cell death and can be initiated by signals originating outside or inside the cell. Apoptosis is thought to play a significant role in the development of HF⁷⁶ and interference with apoptosis as a mechanism to prevent HF would appear to

Table 4. New Classification of Heart Failure Based on American College of Cardiology/American Heart Association Guidelines⁴⁵

Stage	Definition
A	Patients are at high risk for the development of heart failure (eg, systemic hypertension; coronary artery disease; diabetes mellitus) but no apparent structural abnormality of the heart, and never had symptoms of heart failure
B	Patients have structural abnormality but never had symptoms of heart failure
C	Patients have structural abnormality and current or previous symptoms of heart failure
D	Patients have end-stage symptoms that are refractory to standard treatment

merit investigation. The effectors of apoptosis are a family of cysteine proteases termed caspases that exist as inactive precursors and require proteolytic cleavage for activation. Activated caspases cleave proteins following aspartic acid residues to bring about the cellular processes of programmed cell death.⁷⁷ Caspase activation is regulated by signals from cell surface death receptors, which belong to the tumor necrosis factor (TNF) receptor gene super-family, and intracellular apoptotic activators, such as cytochrome c, released from mitochondria.⁷⁸

Apoptosis is associated with postinfarction ventricular remodeling in animal and human MI^{79,80} and is thought to contribute to the transition from compensatory concentric left ventricular hypertrophy to decompensated eccentric failure.⁷⁶ Apoptosis is present in both the infarcted and noninfarcted myocardium and correlates with unfavorable left ventricular remodeling and the development of postischemic HF.⁷⁹

The association between apoptosis and HF suggests that it could represent a valuable therapeutic target in the disorder. Experimental antiapoptotic therapies have been tested to modulate apoptosis in myocardial ischemia.⁸¹⁻⁸³

Although conceptually logical, therapeutic modulation of apoptosis is still in its infancy. The methods to detect apoptosis need to be improved. Further, the spectrum, duration, and temporal changes of apoptosis in myocardial ischemia remain undefined.

MYOCARDIAL REPLACEMENT THERAPY

Although myocardial replacement therapy is a biologic rather than a pharmacologic treatment, it is a promising intervention on the horizon for treatment of postinfarction HF.⁸⁴ Stem cell implants exhibit regenerative properties in damaged tissues, including damaged myocardium.⁸⁴ Only autologous bone marrow cells and tissue stem cells, such as skeletal myoblasts, are currently being investigated as candidates for myocardial regeneration⁸⁵; the use of embryonic stem cells has been restricted due to ethical concerns.

Experimental and clinical trials have demonstrated viability and contractility of engrafted cells and improvements in myocardial perfusion and left ventricular function following transplantation of skeletal myoblasts and bone marrow cells.⁸⁶⁻⁸⁸ The route of cell delivery includes direct intramyocardial injection,^{88,89} catheter-based transmyocardial injection,⁹⁰ and intracoronary infusion.^{91,92} However, a major concern has been the occurrence of ventricular arrhythmias, occasionally requiring implantable cardioverter-defibrillator placement.⁹³

Cell transplantation appears to be a technically and clinically feasible approach for myocardial repair. However, further studies are needed to define the most effective cell type for transplantation, an efficient method for in vitro cell expansion, the optimal timing of postinfarction implantation, and the most effica-

cious mode of cell delivery, as well as methods to minimize adverse effects following transplantation.

CONCLUSION

Previous pharmacologic therapy of HF aimed at reducing the direct modes of HF mortality, progressive cardiac failure, and sudden cardiac death. This approach failed but facilitated an enhanced understanding of the compensatory neurohormonal mechanisms operative in HF. Antagonizing this neurohormonal cascade has been the focus of recent clinical trials. Future directions in HF therapy are likely to focus on limiting or preventing activation of the neurohormonal cascade through earlier recognition and treatment of patients at risk for HF.

REFERENCES

1. Khand A, Gemmel I, Clark AL, Cleland JG. Is the prognosis of heart failure improving? *J Am Coll Cardiol*. 2000; 36:2284-2286.
2. Durand JB. Heart failure management in African Americans: meeting the challenge. *J Clin Hypertens (Greenwich)*. 2004;6(suppl. 1):42-47.
3. Hogg K, Swedberg K, McMurray JJ. Heart failure with preserved left ventricular systolic function. Epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol*. 2004;43:317-327.
4. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation*. 1993; 88:107-115.
5. Cohn JN, Rector TS. Prognosis of congestive heart failure and predictors of mortality. *Am J Cardiol*. 1988;62:25A-30A.
6. O'Connor CM, Gattis WA, Uretsky BF, et al. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). *Am Heart J*. 1999;138(1, pt 1):78-86.
7. Hampton JR, van Veldhuisen DJ, Kleber FX, et al. Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators. *Lancet*. 1997;349:971-977.
8. Xamoterol in severe heart failure. The Xamoterol in Severe Heart Failure Study Group. *Lancet*. 1990;336:1-6.
9. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. *N Engl J Med*. 1991;325:1468-1475.
10. Cohn JN, Goldstein SO, Greenberg BH, et al. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. Vesnarinone Trial Investigators. *N Engl J Med*. 1998;339:1810-1816.
11. Lubsen J, Just H, Hjalmarsson AC, et al. Effect of pimobendan on exercise capacity in patients with heart failure: main results from the Pimobendan in Congestive Heart Failure (PICO) trial. *Heart*. 1996;76:223-231.
12. The effect of digoxin on mortality and morbidity in patients with heart failure. The Digitalis Investigation Group. *N Engl J Med*. 1997;336:525-533.
13. Effects of encainide, flecainide, imipramine and moricizine on ventricular arrhythmias during the year after acute myocardial infarction: the CAPS. The Cardiac Arrhythmia Pilot Study (CAPS) Investigators. *Am J Cardiol*. 1988;61:501-509.

14. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. *N Engl J Med.* 1989;321:406-412.
15. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. The Cardiac Arrhythmia Suppression Trial II Investigators. *N Engl J Med.* 1992;327:227-233.
16. Waldo AL, Camm AJ, deRuyter H, et al. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. Survival With Oral d-Sotalol. *Lancet.* 1996;348:7-12.
17. Julian DG, Camm AJ, Frangin G, et al. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. European Myocardial Infarct Amiodarone Trial Investigators. *Lancet.* 1997;349:667-674.
18. Cairns JA, Connolly SJ, Roberts R, Gent M. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. *Lancet.* 1997;349:675-682.
19. Connolly SJ. Evidence-based analysis of amiodarone efficacy and safety. *Circulation.* 1999;100:2025-2034.
20. Floras JS. Clinical aspects of sympathetic activation and parasympathetic withdrawal in heart failure. *J Am Coll Cardiol.* 1993;22[4, suppl A]:72A-84A.
21. Hirsch AT, Pinto YM, Schunkert H, Dzau VJ. Potential role of the tissue renin-angiotensin system in the pathophysiology of congestive heart failure. *Am J Cardiol.* 1990;66:22D-30D; discussion 30D-32D.
22. Francis GS, Goldsmith SR, Levine TB, Olivari MT, Cohn JN. The neurohumoral axis in congestive heart failure. *Ann Intern Med.* 1984;101:370-377.
23. Wilkins MR, Redondo J, Brown LA. The natriuretic-peptide family. *Lancet.* 1997;349:1307-1310.
24. Underwood R, Chan D, Burnett J. Endothelin: an endothelium derived vasoconstrictor peptide and its role in congestive heart failure. *Heart Fail.* 1991;7:50-58.
25. Sutton MG, Sharpe N. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. *Circulation.* 2000;101:2981-2988.
26. Eichhorn EJ, Bristow MR. Medical therapy can improve the biological properties of the chronically failing heart. A new era in the treatment of heart failure. *Circulation.* 1996;94:2285-2296.
27. Felker G, O'Connor CM. Inotropic therapy for heart failure: an evidence-based approach. *Am Heart J.* 2001;142:393-401.
28. Jessup M, Brozena S. Heart failure. *N Engl J Med.* 2003;348:2007-2018.
29. Group TCTS. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med.* 1987;316:429-435.
30. Investigators TS. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med.* 1991;325:293-302.
31. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med.* 1992;327:669-677.
32. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. *Lancet.* 1993;342:821-828.
33. Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *N Engl J Med.* 1995;333:1670-1676.
34. Group M-HS. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet.* 1999;353:2001-2006.
35. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med.* 1996;334:1349-1355.
36. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med.* 2001;345:1667-1675.
37. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med.* 2003;349:1893-1906.
38. McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet.* 2003;362:767-771.
39. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med.* 1999;341:709-717.
40. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med.* 2003;348:1309-1321.
41. Loeb HS, Johnson G, Henrick A, et al. Effect of enalapril, hydralazine plus isosorbide dinitrate, and prazosin on hospitalization in patients with chronic congestive heart failure. The VHeFT VA Cooperative Studies Group. *Circulation.* 1993;87[6, suppl]:VI78-87.
42. Cody RJ. Approach to the patient with heart failure. In: Humes HD, DuPont HL, Gardner LB, et al, eds. *Kelly's Textbook of Internal Medicine.* 4th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2000.
43. Khalil ME, Basher AVW, Brown EJ Jr, Alhaddad IA. A remarkable medical story: benefits of angiotensin-converting enzyme inhibitors in cardiac patients. *J Am Coll Cardiol.* 2001;37:1757-1764.
44. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA.* 1995;273:1450-1456.
45. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult. Available at: http://acc.org/clinical/guidelines/failure/hf_index.htm. Accessed December 15, 2003.
46. Webster M, Fitzpatrick M, Nicholas M, Ikram H, Wells J. Effects of enalapril on ventricular arrhythmias in congestive heart failure. *Am J Cardiol.* 1985;56:566-569.
47. Nickerson M, Collier B. Drugs inhibiting adrenergic nerves and structures innervated by them. In: Goodman L, Gilman A, eds. *The Pharmacological Basis of Therapeutics.* 5th ed. New York: MacMillan Publishing Co, Inc; 1975:550-552.
48. Foody JM, Farrell MH, Krumholz HM. beta-Blocker therapy in heart failure: scientific review. *JAMA.* 2002;287:883-889.
49. Farrell MH, Foody JM, Krumholz HM. beta-Blockers in heart failure: clinical applications. *JAMA.* 2002;287:890-897.
50. Campbell D, Aggarwal A, Esler M, Kaye D. Beta-blockers, angiotensin II, and ACE inhibitors in patients with heart failure. *Lancet.* 2001;358:1609-1610.
51. Havranek EP, Thomas I, Smith WB, et al. Dose-related beneficial long-term hemodynamic and clinical efficacy of irbesartan in heart failure. *J Am Coll Cardiol.* 1999;33:1174-1181.
52. Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet.* 1997;349:747-752.
53. Packer M, Califf RM, Konstam MA, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation.* 2002;106:920-926.

54. Swedberg K, Bristow MR, Cohn JN, et al. Effects of sustained-release moxonidine, an imidazoline agonist, on plasma norepinephrine in patients with chronic heart failure. *Circulation*. 2002;105:1797-1803.
55. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. Beta-blocker Evaluation of Survival Trial Investigators. *N Engl J Med*. 2001;344:1659-1667.
56. Williams ES, Miller JM. Results from late-breaking clinical trial sessions at the American College of Cardiology 51st Annual Scientific Session. *J Am Coll Cardiol*. 2002;40:1-18.
57. Deswal A, Bozkurt B, Seta Y, et al. Safety and efficacy of a soluble P75 tumor necrosis factor receptor (Enbrel, etanercept) in patients with advanced heart failure. *Circulation*. 1999;99:3224-3226.
58. Coletta AP, Clark AL, Banarjee P, Cleland JG. Clinical trials update: RENEWAL (RENAISSANCE and RECOVER) and ATTACH. *Eur J Heart Fail*. 2002;4:559-561.
59. Coats AJ. Heart Failure 99, the MOXCON story. *Int J Cardiol*. 1999;271:109-111.
60. Bristow MR. Baseline and three month change in systemic venous norepinephrine as predictor of clinical outcome in the BEST trial. *J Am Coll Cardiol*. 2001;37:648A.
61. Mehra MR, Uber PA, Francis GS. Heart failure therapy at a crossroad: are there limits to the neurohormonal model? *J Am Coll Cardiol*. 2003;41:1606-1610.
62. Francis GS, Benedict C, Johnstone DE, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). *Circulation*. 1990;82:1724-1729.
63. Sawyer D, Colucci W. Molecular and cellular events in myocardial hypertrophy and failure. In: Colucci W, ed. *Atlas of Heart Failure, Cardiac Function and Dysfunction*. Singapore: Current Medicine, Inc; 1999:4.2-5.2.
64. Weyman AE. The year in echocardiography. *J Am Coll Cardiol*. 2004;43:140-148.
65. Miller JG, Perez JE, Sobel BE. Ultrasonic characterization of myocardium. *Prog Cardiovasc Dis*. 1985;28:85-110.
66. Di Bello V, Giorgi D, Talini E, et al. Incremental value of ultrasonic tissue characterization (backscatter) in the evaluation of left ventricular myocardial structure and mechanics in essential arterial hypertension. *Circulation*. 2003;107:74-80.
67. Nakae I, Mitsunami K, Omura T, et al. Proton magnetic resonance spectroscopy can detect creatine depletion associated with the progression of heart failure in cardiomyopathy. *J Am Coll Cardiol*. 2003;42:1587-1593.
68. Braunwald E. The Simon Dack lecture. Cardiology: the past, the present, and the future. *J Am Coll Cardiol*. 2003;42:2031-2041.
69. Baliga RR, Narula J. Pharmacogenomics of congestive heart failure. *Med Clin North Am*. 2003;87:569-578.
70. Psaty BM, Smith NL, Heckbert SR, et al. Diuretic therapy, the alpha-adducin gene variant, and the risk of myocardial infarction or stroke in persons with treated hypertension. *JAMA*. 2002;287:1680-1689.
71. Small KM, Wagoner LE, Levin AM, Kardias SL, Liggett SB. Synergistic polymorphisms of beta1- and alpha2C-adrenergic receptors and the risk of congestive heart failure. *N Engl J Med*. 2002;347:1135-1142.
72. Wang L, Fan C, Topol SE, Topol EJ, Wang Q. Mutation of MEF2A in an inherited disorder with features of coronary artery disease. *Science*. 2003;302:1578-1581.
73. Razeghi P, Young ME, Cockrill TC, Frazier OH, Taegtmeyer H. Downregulation of myocardial myocyte enhancer factor 2C and myocyte enhancer factor 2C-regulated gene expression in diabetic patients with nonischemic heart failure. *Circulation*. 2002;106:407-411.
74. Yamada Y, Izawa H, Ichihara S, et al. Prediction of the risk of myocardial infarction from polymorphisms in candidate genes. *N Engl J Med*. 2002;347:1916-1923.
75. Ciccoira M, Zanolla L, Rossi A, et al. Failure of aldosterone suppression despite angiotensin-converting enzyme (ACE) inhibitor administration in chronic heart failure is associated with ACE DD genotype. *J Am Coll Cardiol*. 2001;37:1808-1812.
76. Matturri L, Milei J, Grana DR, Lavezzi AM. Characterization of myocardial hypertrophy by DNA content, PCNA expression and apoptotic index. *Int J Cardiol*. 2002;82:33-39.
77. Thornberry NA, Lazebnik Y. Caspases: enemies within. *Science*. 1998;281:1312-1316.
78. Ashkenazi A, Dixit VM. Death receptors: signaling and modulation. *Science*. 1998;281:1305-1308.
79. Abbate A, Biondi-Zoccai GG, Bussani R, et al. Increased myocardial apoptosis in patients with unfavorable left ventricular remodeling and early symptomatic post-infarction heart failure. *J Am Coll Cardiol*. 2003;41:753-760.
80. Palojoki E, Saraste A, Eriksson A, et al. Cardiomyocyte apoptosis and ventricular remodeling after myocardial infarction in rats. *Am J Physiol Heart Circ Physiol*. 2001;280:H2726-2731.
81. Morishita R, Sugimoto T, Aoki M, et al. In vivo transfection of cis element "decoy" against nuclear factor-kappaB binding site prevents myocardial infarction. *Nat Med*. 1997;3:894-899.
82. Kirshenbaum LA, de Moissac D. The bcl-2 gene product prevents programmed cell death of ventricular myocytes. *Circulation*. 1997;96:1580-1585.
83. Okamura T, Miura T, Takemura G, et al. Effect of caspase inhibitors on myocardial infarct size and myocyte DNA fragmentation in the ischemia-reperfused rat heart. *Cardiovasc Res*. 2000;45:642-650.
84. Hagege AA, Vilquin JT, Bruneval P, Menasche P. Regeneration of the myocardium: a new role in the treatment of ischemic heart disease? *Hypertension*. 2001;38:1413-1415.
85. Siminiak T, Kurpisz M. Myocardial replacement therapy. *Circulation*. 2003;108:1167-1171.
86. Fuchs S, Baffour R, Zhou YF, et al. Transendocardial delivery of autologous bone marrow enhances collateral perfusion and regional function in pigs with chronic experimental myocardial ischemia. *J Am Coll Cardiol*. 2001;37:1726-1732.
87. Jain M, DerSimonian H, Brenner DA, et al. Cell therapy attenuates deleterious ventricular remodeling and improves cardiac performance after myocardial infarction. *Circulation*. 2001;103:1920-1927.
88. Stamm C, Westphal B, Kleine HD, et al. Autologous bone-marrow stem-cell transplantation for myocardial regeneration. *Lancet*. 2003;361:45-46.
89. Menasche P, Hagege AA, Scorsin M, et al. Myoblast transplantation for heart failure. *Lancet*. 2001;357:279-280.
90. Smits PC, van Geuns RJ, Poldermans D, et al. Catheter-based intramyocardial injection of autologous skeletal myoblasts as a primary treatment of ischemic heart failure: clinical experience with six-month follow-up. *J Am Coll Cardiol*. 2003;42:2063-2069.
91. Strauer BE, Brehm M, Zeus T, et al. Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans. *Circulation*. 2002;106:1913-1918.
92. Assmus B, Schachinger V, Teupe C, et al. Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI). *Circulation*. 2002;106:3009-3017.
93. Menasche P, Hagege AA, Vilquin JT, et al. Autologous skeletal myoblast transplantation for severe postinfarction left ventricular dysfunction. *J Am Coll Cardiol*. 2003;41:1078-1083.