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STATE-OF-THE-ART PAPER

CME

Heart Failure

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JACC: HEART FAILURE CME

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CME Objective for This Article: After reading this article, the reader should understand: 1) the epidemiology of heart failure including risk factors, associated morbidity and mortality, and costs to the healthcare system; 2) heart failure pathophysiology models; and 3) recent developments in the management of heart failure.

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Heart Failure

Despite major improvements in the treatment of virtually all cardiac disorders, heart failure (HF) is an exception, in that its prevalence is rising, and only small prolongations in survival are occurring. An increasing fraction, especially older women with diabetes, obesity, and atrial fibrillation exhibit HF with preserved systolic function. Several pathogenetic mechanisms appear to be operative in HF. These include increased hemodynamic overload, ischemia-related dysfunction, ventricular remodeling, excessive neurohumoral stimulation, abnormal myocyte calcium cycling, excessive or inadequate proliferation of the extracellular matrix, accelerated apoptosis, and genetic mutations. Biomarkers released as a consequence of myocardial stretch, imbalance between formation and breakdown of extracellular matrix, inflammation, and renal failure are useful in the identification of the pathogenetic mechanism and, when used in combination, may become helpful in estimating prognosis and selecting appropriate therapy. Promising new therapies that are now undergoing intensive investigation include an angiotensin receptor neprilysin inhibitor, a naturally-occurring vasodilator peptide, a myofilament sensitizer and several drugs that enhance Ca^{++} uptake by the sarcoplasmic reticulum. Cell therapy, using autologous bone marrow and cardiac progenitor cells, appears to be promising, as does gene therapy. Chronic left ventricular assistance with continuous flow pumps is being applied more frequently and successfully as destination therapy, as a bridge to transplantation, and even as a bridge to recovery and explantation. While many of these therapies will improve the care of patients with HF, significant reductions in prevalence will require vigorous, multifaceted, preventive approaches. (J Am Coll Cardiol HF 2013;1:1–20) © **2013 by the American College of Cardiology Foundation**

Epidemiology

During the past half-century, the advances in the prevention, diagnosis, and management of cardiovascular disease (CVD) have been nothing short of spectacular. Age-adjusted CVD-related deaths have declined by about two-thirds in industrialized nations (1). Mortality rates associated with the acute coronary syndromes (ACS), valvular and congenital heart disease, uncontrolled hypertension, and many arrhythmias all have fallen dramatically.

Heart failure (HF) is a notable exception to these encouraging trends. Indeed, after normal delivery, it is the most common cause of hospitalization. Annual hospital discharges in patients with a primary diagnosis of HF have risen steadily since 1975, and now exceed 1 million discharges per year, although they may at last be leveling off (2,3) (Fig. 1), or actually decreasing, in the United States (4,5). In Europe, hospitalizations for HF are clearly declining (6,7). HF is primarily a disease of the elderly that affects about 10% of men and 8% of women over the age of 60 years, and its prevalence rises with age (Fig. 2) and has risen overall. In the United States, patients with a primary diagnosis of HF now make >3 million physician visits per year. The direct and indirect costs of HF in the United States are staggering; in 2010 they were estimated to be US $39.2 billion (8). The estimated lifetime cost of HF per individual patient is $110,000/year (-2008 US dollars), with more than three-fourths of this cost consumed by in-hospital care (9).

Survival after a diagnosis of HF has improved during the past 30 years; the age-adjusted death rate has declined (4–6), and the mean age at death from HF has risen (7,10). However, despite these modest improvements, the 5-year mortality is still approximately 50%—worse than that of many cancers (11). Among Medicare patients, 30-day mortality is 10% to 12% (12), and the 30-day readmission rate after hospital discharge is 20% to 25% (13).

How can this so-called "HF paradox"—that is, the striking improvements in the prognosis of individual cardiac conditions, such as ACS, severe hypertension, valvular and congenital heart diseases, but a growing prevalence of HF—be explained? Three possibilities warrant consideration. The first is that, while the risk for mortality in each of these disorders has been reduced, the patients are not "cured" (with the exception of those with certain congenital malformations). For example, while early mortality in patients with acute myocardial infarction may have declined by 75% during the past half-century (14), survivors still have coronary artery disease (CAD) and remain at risk for subsequent episodes of ischemic myocardial damage with further loss of myocardium and possibly HF. A second possible explanation may be related to the increased frequency of myocyte death with aging and with the adverse cardiac consequences of comorbid conditions, the prevalences of which rise with age. These comorbid conditions include hypertension; type 2 diabetes mellitus; chronic renal disease; chronic obstructive pulmonary disease; and dysrhythmias, especially atrial fibrillation (15). The third possible explanation is that the slow but progressive improvement in HF prognosis mentioned previously simply increases the prevalence of this condition. Whatever the explanation(s), one might conclude that with the continued aging of the population, HF will remain a major health problem, not only in industrialized nations but also in the developing world.

Given this magnitude, attention is being directed, appropriately, to identifying individuals at higher risk for HF. Risk factors include increased body mass index, abdominal fat accumulation, elevated fasting blood glucose, elevated systolic blood pressure, elevated apolipoprotein B/apolipoprotein A ratio, and cigarette smoking. In a large-scale (1 million person-years) study that included both outpatients and inpatients from all age groups in an insured

population in Georgia, CAD, hypertension, diabetes, and valvular heart disease most frequently preceded the diagnosis of HF (16).

The clinical–hemodynamic profile of patients with HF appears to be changing (10). In a registry of >110,000 patients hospitalized with HF, the proportion with heart failure and a preserved ejection fraction (HFPEF), usually defined as an EF >50%, was approximately 40%, and in-hospital mortality was only slightly lower than that in patients with HF and reduced EF (HFREF) (17). Also, a smaller percentage of patients with HFPEF than of patients with HFREF die from CVD-related causes (18). As a group, HFPEF patients are older and more commonly female, with greater hypertension, obesity, anemia, and atrial fibrillation compared to those with HFREF (19). Diastolic dysfunction may remain asymptomatic for years, but age, renal dysfunction, hypertension, and progression of this dysfunction all appear to be associated with the development of overt HF in this population (20,21).

Acute decompensation heart failure (ADHF), that is, the new onset of severe HF or the sudden intensification of chronic HF, is a life-threatening condition that usually requires hospitalization and is, in fact, the most common cause of hospital admission among patients with HF. ADHF may result from 1 or more precipitating events, including the development of a variety of dysrhythmias; ACS; a rapid increase in the need for an increased cardiac output of the failing heart by conditions such as infection, anemia, and pulmonary thromboembolism superimposed on chronic HF (22); discontinuation of treatment of chronic HF; and progression of the underlying disease. Based on data from >100,000 hospitalizations in ADHERE (Acute Decompensated Heart Failure National Registry), a simple prognostic tool was established with findings that can be obtained easily at presentation. In a multivariate analysis, elevations in age, blood urea nitrogen, creatinine, and heart rate; lower systolic pressure and serum sodium; the presence of dyspnea at rest; and the lack of long-term treatment with a β-blocker were identified as independent predictors of mortality (23).

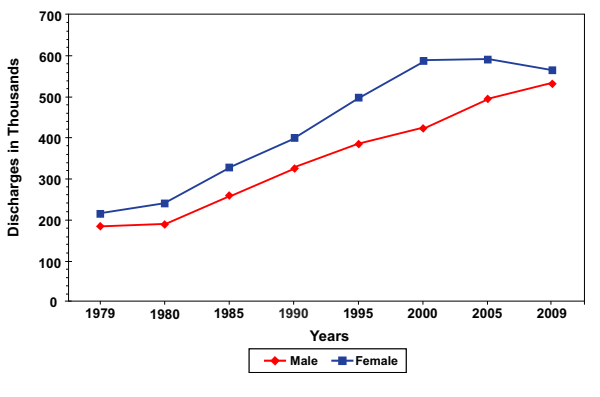

Figure 1 **Discharges From Hospitalization Due to Heart Failure, by Sex (United States, 1979–2009)**

Reprinted with permission from: Roger VL, Go AS, Lloyd-Jones DM et al. Heart disease and stroke statistics—2012 update. Circulation 2012;125:e12–30. Source: National Hospital Discharge Survey/National Center for Health Statistics and National Heart, Lung, and Blood Institute.

Mechanisms

The mechanisms involved in HF have been investigated from a variety of perspectives during the past half-century. These perspectives have sometimes been referred to as "models" (24).

Hemodynamic model. In 1967, the author and his colleagues defined HF as "a clinical syndrome characterized by well known symptoms and physical signs. . . . [It is] the pathological state in which an abnormality of myocardial function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues during ordinary activity" (25). Support for this hemodynamic model of HF came from the observation that, in HF resulting from absolute or relative increases in hemodynamic load, there is actually a reduction in the intrinsic contractility of cardiac muscle. This was reflected in a reduction in force development of isolated cardiac muscle obtained from the failing hearts of experimental animal preparations with pressure overload (26) and then from isolated myocytes obtained from patients with HFREF (27).

Important hemodynamic changes in HF result from ventricular remodeling, which is common in patients with chronic dysfunction of the ventricular pump, and which varies by HF type (28). In patients with HFPEF, the volume of the left-ventricular (LV) cavity is typically normal, but the wall is thickened, and the ratios of LV mass/end-diastolic volume and the myocardial stiffness modulus are both increased (29). In contrast, in patients with HFREF, the LV cavity is typically

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ACS = acute coronary syndromes
ADHF = acute decompensation heart failure
ANP = atrial natriuretic peptide
ARB = angiotensin II receptor blocker
BNP = brain natriuretic peptide
CAD = coronary artery disease
CPC = cardiac stem/progenitor cell
CRP = C-reactive protein
cTn = cardiac-specific troponin
CVD = cardiovascular disease
ECM = extracellular matrix
EF = ejection fraction
HF = heart failure
HFPEF = heart failure and a preserved ejection fraction
HFREF = heart failure and a reduced ejection fraction
hs = high-sensitivity
LV = left-ventricular
LVAD = left-ventricular assist device
miR = micro RNA
MMP = matrix metalloproteinases
NP = natriuretic peptide
NT-proBNP = N-terminal pro-B-type natriuretic peptide
PINP = pro collagen type I aminoterminal propeptide
PIIINP = collagen III N-terminal propeptide
RyR2 = ryanodine receptor
SR = sarcoplasmic reticulum
SERCA2a = sarcoplasmic reticulum Ca^{2+} adenosine triphosphatase

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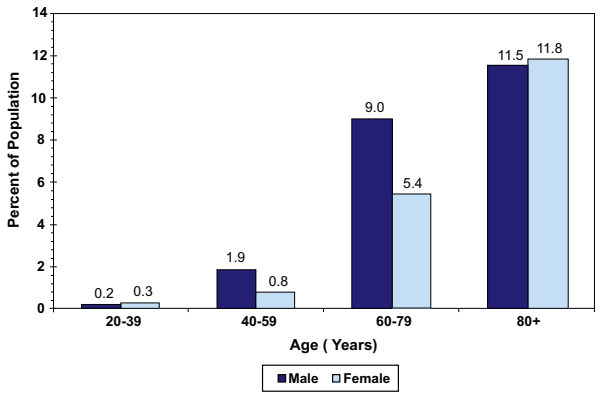

Figure 2 **Prevalence of Heart Failure, by Sex and Age (National Health and Nutrition Examination Survey, 2005–2008)**

Reprinted with permission from: Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2012 update. Circulation 2012;125:e12–30. Source: National Hospital Discharge Survey/National Center for Health Statistics and National Heart, Lung, and Blood Institute.

dilated, and there is either a normal or reduced ratio of LV mass/end-diastolic volume. At the cellular level, both cardiomyocyte diameter and myofibrillar density are higher in HFPEF than in HFREF (30).

EXTRACELLULAR MATRIX. The size, shape, and thickness of the extracellular matrix (ECM) are important determinants of the architecture of the intact ventricles and thereby their pumping function. The ECM can be thought of as a scaffolding, or internal skeleton, of the ventricles (31). Remodeling of the ECM occurs with replacement fibrosis following myocardial infarction, a process that has been referred to as a "morphologic footprint of earlier myocardial necrosis" (32). Myocardial necrosis enhances the release of growth factors in the connective tissue, which results in the formation of new fibroblasts. When this process is inadequate, such as after infarction, there is thinning of the ventricular wall, possible ventricular aneurysm formation, and further impairment of LV pump function. The increased synthesis of ECM enhances myocardial stiffness in pressure overload hypertrophy and reduces the rate of ventricular relaxation (and filling) as well as contraction (emptying) (33). Fibrosis can be stimulated by long-term activation of the renin-angiotensin-aldosterone system, especially by aldosterone (34).

Matrix metalloproteinases (MMPs) are a family of zinc-dependent enzymes involved in the degradation of the ECM. Their activity can be inhibited by a group of proteins termed tissue inhibitors of MMP. The myocardial fibrosis consequent to myocardial infarction and pressure-load hypertrophy may be associated with changes in ECM degradation resulting from an imbalance between MMPs and tissue inhibitors of MMPs, favoring the latter, and causing excessive fibrosis. Conversely, overexpression of MMPs may play an important role in ventricular remodeling in patients with dilated cardiomyopathy as well as in patients with ventricular volume overload states such as valvular regurgitation (31). Both imbalances can affect hemodynamics adversely.

Cardiorenal model. Renal sodium and water retention are integral components of the HF syndrome because they play a crucial role in the genesis of dyspnea and edema, 2 cardinal clinical manifestations of the syndrome. This consideration led to the cardiorenal model of HF, which emphasizes the close interplay between these 2 organ systems. Both diuretics and dietary sodium restriction are crucial to the management of congestion in patients with HF. However, when such therapy is intensified in patients with severe HF, it may lead to renal failure (the cardiorenal syndrome), a condition that is associated with a high mortality rate.

Neurohumoral model. In the 1960s, it became clear that, in healthy subjects, activation of the adrenergic nervous system is an important regulator of cardiac performance during exertion; it increases myocardial contractility and redistributes cardiac output (25,35) (Fig. 3). In acute HF, enhanced contractility resulting from adrenergic activation stimulates the depressed contractility of the failing heart and, by causing vasoconstriction, raises the blood pressure and aids in the perfusion of vital organs. However, prolonged

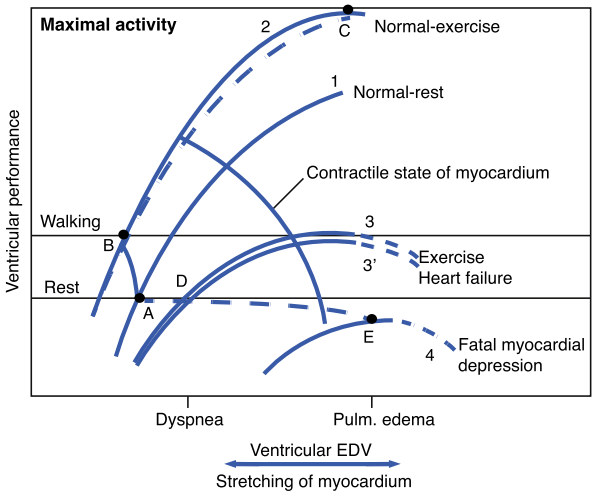

Figure 3 **Influences on Ventricular EDV Through Stretching of the Myocardium and the Contractile State of the Myocardium**

Levels of ventricular end-diastolic volume (EDV) associated with filling pressures that result in dyspnea and pulmonary edema are shown on the abscissa. Levels of ventricular performance required during rest, light activity (walking), and maximal activity are on the ordinate. The **dashed lines** are the descending limbs of the ventricular performance curves, which are rarely seen during life but show the level of ventricular performance if EDV could be elevated to very high levels. A = normal at rest; B = normal walking; C = normal maximal exercise; D = heart failure at rest; E = heart failure while walking. Reprinted with permission from Braunwald E: Normal and abnormal myocardial function. In Braunwald E, et al. [eds]: Harrison's Principles of Internal Medicine, 15th ed. New York: McGraw-Hill, 2001:1309–18, as modified from Braunwald E, Ross J Jr., Sonnenblick EH: *Mechanisms of Contraction of the Normal and Failing Heart.* Boston: Little, Brown; 1978.

activation of the adrenergic nervous system and of the renin-angiotensin-aldosterone system causes maladaptive remodeling of the ventricles and further myocardial injury, thereby initiating a vicious cycle in what has become known as the neurohumoral model of HF. The importance of this model became even clearer when it was discovered that blockade of these 2 systems prolongs survival in patients with HF (Fig. 4).

Abnormal Ca^{2+} cycling model. Cardiac contraction results from the interaction of the thick (myosin) and thin (actin) myofilaments; this interaction is triggered by the cytoplasmic [Ca^{2+}]. The importance of Ca^{2+} to cardiac contraction has been appreciated since the classic experiments described by Ringer in 1883 (36). In the abnormal calcium cycling model of HF, dysregulation of Ca^{2+} fluxes are considered central to the depression of the myocardial contractility that occurs in certain types of HF (Fig. 5). During depolarization of the cell membrane, Ca^{2+} enters the myocyte through L-type Ca^{2+} channels located in the indentations of the membrane known as transverse tubules, which are in close proximity to the sarcoplasmic reticulum (SR). This influx stimulates the release of much greater quantities of Ca^{2+} from the SR into the cytoplasm through the Ca^{2+} release channels, also known as the ryanodine receptors (RyR2).

After reaching a critical concentration, the cytoplasmic Ca^{2+} activates the contractile system of the myocyte, thereby triggering contraction. The sarcoendoplasmic reticular adenosine triphosphate–driven [Ca^{2+}] pump (SERCA2a) returns cytoplasmic Ca^{2+} to the SR against a concentration gradient. This reduction in cytoplasmic [Ca^{2+}] shuts off contraction and initiates myocyte relaxation (Fig. 6).

Dysregulation of Ca^{2+} movements has been demonstrated in certain types of HF. A diastolic leak of Ca^{2+} through altered RyR2 lowers the Ca^{2+} content of the SR, reducing the Ca^{2+} that can be released during activation, thereby weakening contraction (37). While there is agreement that abnormal function of these receptors occurs in certain types of HF, there is controversy regarding the molecular cause of "leaky" RyR2 receptors. Some have attributed it to hyperphosphorylation of this receptor at serine 2808 by phosphokinase A (38); others, to the phosphorylation of a nearby amino acid, serine 2814, by another enzyme, Ca^{2+}/calmodular-dependent protein kinase II (39).

A second major abnormality of Ca^{2+} fluxes that may play a crucial role in the development of HF is a loss of function of the SERCA2a pump, which reduces the Ca^{2+} content of the cardiac SR and hence the quantity of this ion that can be released during myocyte activation, causing systolic dysfunction and ventricular tachyarrhythmias (40). This defect in SERCA2a function also reduces the quantity and speed of removal of Ca^{2+} from the cytoplasm, thereby inhibiting ventricular relaxation and causing diastolic dysfunction. Phospholamban is a protein that is in close proximity to and regulates SERCA2a (Fig. 6). In the dephosphorylated state, phospholamban inhibits SERCA2a. Stimulation of β-adrenergic receptors normally causes the phosphorylation of phospholamban and thereby disinhibits (stimulates) SERCA2a, enhancing both cardiac contraction and relaxation (Fig. 6). This "contractile reserve" provided by adrenergic stimulation may be reduced in HF, with the desensitization of myocardial β-receptors that occurs in this condition (41).

Cell death model. All types of HF are characterized by an increased rate of cell death (42), which has been attributed to a variety of stresses, including abnormal elevations in circulating neurohormones; excessive adrenergic activity; inflammation; oxidative stress; toxins, such as alcohol or cancer chemotherapeutic agents; and infiltrative processes. Apoptosis is a highly regulated type of cell death that normally increases with aging and is further accelerated in the presence of pressure overload. It has been suggested that, over time, the resulting deletion of myocytes leads to HF (43). Myocardial necrosis, the dominant type of cell death in myocardial infarction, also occurs in doxorubicin-induced and other toxic cardiomyopathies (42), as well as in Ca^{2+}-induced mitochondrial damage, which occurs during reperfusion following severe ischemia (44). In autophagy, cells digest their own intracellular proteins and lipids, a process that may be normal (protective) when these substances are altered and become toxic, but when accelerated may become maladaptive and result in increased cell death (45).

Genetic model. Until about 5 years ago, the search for genes associated with specific diseases (including CVD) focused

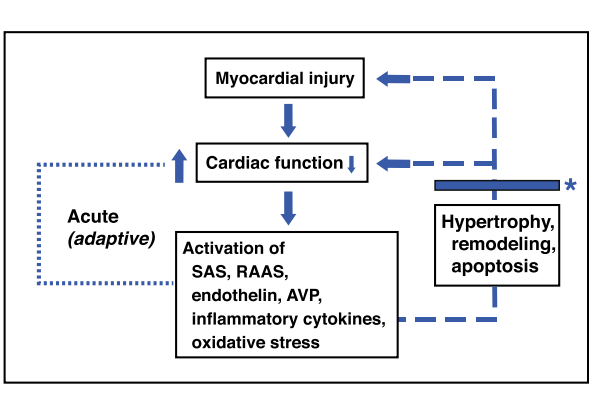

Figure 4 **Interplay Between Cardiac Function and Neurohumoral and Cytokine Systems**

Myocardial injury, which may have any of a number of causes, might depress cardiac function, which in turn may cause activation of the sympathoadrenal system and the renin-angiotensin-aldosterone system and the elaboration of endothelin, arginine vasopressin, and cytokines such as tumor necrosis factor (TNF)-α. In acute heart failure **(left),** these are adaptive and tend to maintain arterial pressure and cardiac function. In chronic heart failure **(right),** they cause maladaptive hypertrophic remodeling and apoptosis, which cause further myocardial injury and impairment of cardiac function. The **horizontal line on the right** shows that chronic maladaptive influences can be inhibited by angiotensin-converting enzyme inhibitors, β-adrenergic blockers, angiotensin II type 1 receptor blockers, and/or aldosterone antagonists. Reprinted with permission from Braunwald E. Normal and abnormal myocardial function, In Braunwald E et al. [eds]: Harrison's Principles of Internal Medicine, 15th ed. New York: McGraw-Hill; 2001:1309–18.

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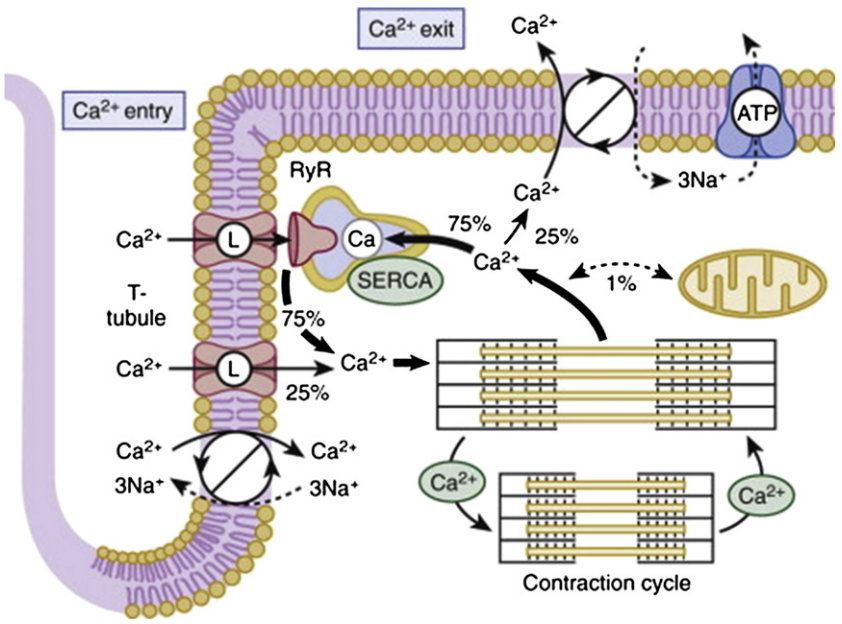

Figure 5 **Calcium Fluxes in the Myocardium**

Calcium ions (Ca^{2+}) enter the cell through L-type Ca^{2+} channels (L), which triggers the release of Ca^{2+} from the sarcoplasmic reticulum to initiate contraction. Ca^{2+} leaves the myocyte via the Na^{+}/Ca^{2+} exchanger. RyR = ryanodine receptors (Ca^{2+} release channels); SERCA = sarcoplasmic reticular adenosine triphosphate (ATP)-driven pump, which returns Ca^{2+} to the sarcoplasmic reticulum (SR). From Opie LH, Hasenfuss G: Mechanisms of cardiac contraction and relaxation. In: Bonow RO, et al. [eds]. Braunwald's Heart Disease, 9th ed. Philadelphia: Elsevier; 2012:459–86. Reprinted with permission from Opie LH. Heart Physiology: From Cell to Circulation. Philadelphia: Lippincott Williams & Wilkins; © DM Bers and LH Opie, 2004; also see Bers DM: Cardiac excitation-contraction coupling. Nature 415:198, 2002.

largely on so-called "candidate genes," which encode the abnormal proteins in diseased hearts. This approach allowed the identification of a number of important monogenic disorders involved in the cardiomyopathies that lead to HF (46,47) and led to the genetic model of HF. Inherited cardiomyopathies are caused by mutations in the genes that encode sarcomeric proteins (hypertrophic cardiomyopathy) (46,48) and/or mutations in the genes that encode diverse proteins causing impaired contraction and cell death (familial dilated cardiomyopathy), including genes for nuclear envelope proteins (49) and desmosomal proteins crucial for intercellular attachments in arrhythmic right-ventricular cardiomyopathy (48).

The current emphasis on genetics is focused on scanning the entire genome in an unbiased manner to search for genetic variants associated with specific diseases using genome-wide association studies (50). Because HF is a syndrome, not a disease, genome-wide association studies in HF are designed to search for loci associated with the conditions that lead to HF, such as CAD, hypertension, hyperlipidemia, and diabetes mellitus (51). A recent analysis identified 13 loci spread throughout the genome that are associated with an increased risk for CAD. Three new genetic loci for dilated cardiomyopathy were recently described (52,53). While this approach and these discoveries are exciting, they represent only the initial step in elucidating the mechanisms by which genetic abnormalities can affect cardiac function and the development of HF. The next challenge will be to link these loci with specific genes and, in turn, with biological function and dysfunction.

An important new chapter in biology opened 20 years ago, when a new regulatory mechanism involving small (~22-nucleotide) RNAs, or micro RNAs (miRs), were described (54). Almost 1,000 of these molecules have been isolated and more are being discovered regularly; they are found in all life forms and are critically important to posttranscriptional gene regulation. Many investigators are currently attempting to gain an understanding of the role of these molecules in health and disease (55). It appears that miRs exert control over processes integral to normal and disordered cardiac function, including excitation–contraction coupling, myocyte hypertrophy, ventricular dilatation, apoptosis, and myocardial fibrosis (56). For example, it has been reported that the absence of miR-22 in genetically altered mice was associated with reduced activity of SERCA2 in the myocytes and with an impaired response to pressure overload (57). In addition to their presence in tissues, miRs may enter the bloodstream, from which they can be isolated and have the potential to become a new class of biomarkers (58) in a number of conditions, including HF. Pharmacologically induced changes in the activity of miRs could become a new class of therapeutics (59).

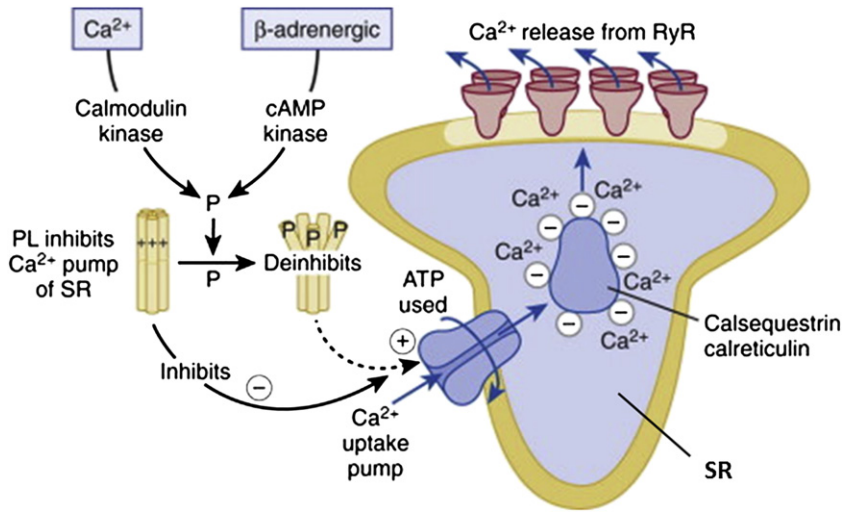

Figure 6 **Mechanism of Ca^{2+} Uptake Into the SR by the ATP-Driven Ca^{2+} Uptake Pump (SERCA2a)**

Within the SR, Ca^{2+} is attached to the protein calsequestrin. An increased rate of uptake of Ca^{2+} into the SR enhances the rate of relaxation (lusitropic effect). Phospholamban (PL), when phosphorylated (P), removes the inhibition exerted on the Ca^{2+} pump by its dephosphorylated form. Thereby, Ca^{2+} uptake is increased either in response to an enhanced cytosolic Ca^{2+} or in response to β-adrenergic stimulation, which activates cyclic adenosine monophosphate (cAMP) kinase. Calmodulin kinase may be a second messenger of the β-adrenergic system. RyR = ryanodine receptor in the Ca^{2+} release channel; other abbreviations as in Figure 5. From Opie LH, Hasenfuss G: Mechanisms of cardiac contraction and relaxation. In: Bonow RO, et al. [eds]. Braunwald's Heart Disease, 9th ed. Philadelphia: Elsevier; 2012, as modified with permission from Opie LH. Heart Physiology, from Cell to Circulation. Philadelphia: Williams & Wilkins; 2004.

Biomarkers

Although the definition of a biomarker includes virtually any measurement that can be made on a biological system, this discussion is restricted to substances measured in the blood other than genetic markers, electrolytes, and commonly used markers of hepatic or renal function. These biomarkers aid in the diagnosis of HF, provide an estimate of prognosis, and help in the identification of apparently healthy people who are at excessive risk for HF (60). Biomarkers that are currently available reflect at least 7 pathobiological processes operative in HF (Fig. 7), help to identify the specific ones involved in individual patients, and aid in guiding management plans. The increased availability of point-of-care and rapid-turnaround methodologies, and the declining costs of analysis of several of the most frequently used biomarkers, are facilitating their widespread use.

In the assessment of the clinical value of any individual biomarker, it is important to determine whether it provides independent incremental information when added to previously available information, which can be estimated by determining whether it increases the *c* statistic (61), as well as by calculating the net reclassification improvement index and the integrated discrimination improvement index (62). Despite the importance of these rigorous statistical tests, measurements of biomarkers, even those that are not independent predictors of risk on multivariate analysis, may nonetheless be of clinical importance because they provide information on the pathogenesis of HF and can help to direct treatment. For example, in patients with abnormally elevated levels of a natriuretic peptide (NP) and troponin, an abnormally elevated concentration of a marker for ECM remodeling might not add discriminatory diagnostic power but might suggest that a drug that reduces collagen deposition may be beneficial (see subsequent discussion).

Markers of myocyte stretch. Atrial NP (ANP) was the first NP elaborated by stretched cardiac tissue to be identified and studied in patients with HF (63). However, because

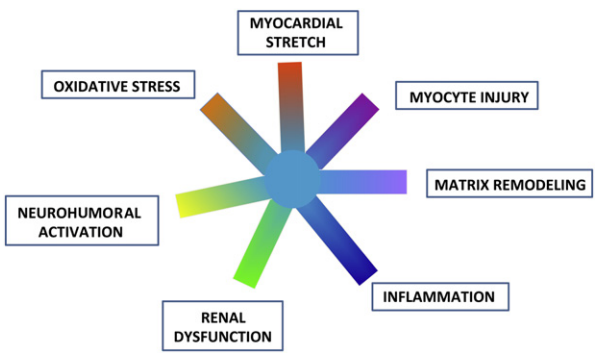

Figure 7 **Seven Major Classes of Biomarkers Contributing to the Biomarker Profile in HF**

Adapted with permission from Braunwald E. Preface. Heart Fail Clin 2009;5:xiii–xiv.

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of its instability and other analytic problems, it was soon replaced by B-type NP (BNP) and its prohormone fragment, N-terminal pro B–type natriuretic peptide (NT-proBNP), peptides derived largely from the ventricles. These 2 peptides are now the most widely used biomarkers in the care of patients with known or suspected HF (64,65). In addition, mid-regional (MR) proANP, a precursor of ANP, does not pose the same analytical problems as does ANP and has been reported to have been as accurate as BNP and NT-proBNP in diagnosing HF (66) and in estimating the prognosis of patients with HF (67). In patients with chronic CAD and normal EF, MR-proANP has also been reported to predict CVD-related death or hospitalization for HF and to identify patients who might benefit from the administration of an angiotensin-converting enzyme (ACE) inhibitor (68).

NPs are of enormous clinical value in diagnosing HF in patients with dyspnea of unknown etiology (64–66,69,70); in patients with heart disease without clinical manifestations of, but who are at risk for, HF; and in apparently healthy patients who are at higher risk for HF (71). However, like any laboratory measurement, NP levels must be interpreted in the context of a patient's characteristics, such as age and body mass, and laboratory tests, including cardiac imaging.

There is some controversy regarding the clinical value of NP-guided therapy for HF (72). However, 2 meta-analyses have reported significant advantages of NP-guided therapy in terms of survival (73,74). In the larger of these (1,726 patients), NP-guided therapy was compared with usual care in 8 moderate-scale trials, and a significantly lower mortality was reported with NP-guided therapy (hazard ratio = 0.76). However, in these trials, NP-guided therapy was of little value in 2 subgroups—patients age >75 years and those with HFPEF. Like all meta-analyses, these were limited by differences in the characteristics of the populations studied, the peptide concentrations targeted, and the treatment algorithms employed. Fortunately, a robust, adequately sized multicenter trial of a single-target NP level and the use of guideline-approved therapies in both treatment arms of prespecified subgroups is now underway (GUIDE-IT [Guiding Evidence Based Therapy Using Biomarker Intensified Treatment]; NCT01685840).

ST2 is a protein that exists in soluble and membrane-bound forms, the latter being the receptor for interleukin 33. When the myocardium is stretched, the *ST2* gene is upregulated, and the concentration of circulating soluble ST2 rises rapidly. The level of circulating ST2 has been reported to be a predictor of HF and death in patients with ST-segment elevation myocardial infarction (75), ADHF, and/or chronic HF (76). This biomarker provides prognostic information that is independent of and in addition to that offered by NT-proBNP (77), although the release of both seems to occur in response to the same stimulus—cardiac stretch.

Myocyte injury. The 2 cardiac-specific troponins (cTn)—I and T (cTnI and cTnT, respectively)—exist in 2 pools in myocytes. The larger is an integral constituent of the myofibrillar protein apparatus and is released slowly over several days after cell death; the second, smaller source of cTn resides in a cytoplasmic pool this is released relatively rapidly, within 1 to 2 hours of myocyte injury. It is not yet clear whether irreversible injury is required or whether reversibly injured cells whose membranes have transiently become more permeable can also release this pool (78).

cTnI and cTnT have become the most accurate and widely used markers of myocardial necrosis in patients with ACS. However, in 1997, it was reported that cTnI is also present in the serum of patients with severe HF without ischemia (79), and it was then observed that levels of cTnI and cTnT were predictive of adverse clinical outcomes in these patients (80). This observation has been amply confirmed, particularly as progressively more sensitive assays for cTn have become available (81,82). The release of troponin from the heart in HF has been considered to be due to myocyte injury, apparently irrespective of the mechanism involved, that is, ischemia, necrosis, apoptosis, or autophagy.

Using standard assays, abnormal elevations of circulating cTn have been reported in about one-quarter of patients with HF and denoted a poor prognosis, generally defined as death or early readmission for HF (60). Using high-sensitivity assays (hsTn), abnormal elevations in circulating troponins have been detected in virtually all patients with ADHF (83–86), in a majority of a population with chronic HF (87), in some patients with stable CAD and normal EF (88), as well as in a minority of general populations of apparently healthy elderly (89) and middle-aged persons (90). Serial measurements of hsTn in populations with ADHF (86) and chronic HF (87) have been reported to provide additional prognostic information; cTn levels that rose during hospitalization portended a poorer outcome than did stable or declining levels.

ECM markers. The importance of the ECMs in ventricular remodeling is discussed in the Mechanisms and Management sections. Serum peptides derived from collagen metabolism reflect both the synthesis and degradation of collagen and thus constitute a "window" on the ECM (91,92). The ratio of pro collagen type I amino-terminal propeptide (PINP), a marker of collagen synthesis, to collagen type I cross-linked carboxyterminal telopeptide, a marker of collagen breakdown, is a useful serum marker of collagen accumulation (93). A multimarker panel consisting of increased levels of MMP-2, tissue inhibitor of MMP-4, and collagen III N-terminal propeptide (PIIINP), accompanied by decreased levels of MMP-8, has been reported to be characteristic of HFPEF (92). Elevated ECM turnover has also been reported in patients with ADHF (91).

Aldosterone is a stimulant of collagen synthesis and enhances cardiac fibrosis in HF and in ventricular hypertrophy secondary to pressure overload. The administration of the aldosterone receptor antagonist spironolactone in patients with chronic HF in RALES (Randomized

Aldactone Evaluation Study) reduced elevated levels of markers of collagen synthesis (PINP and PIIINP) and was associated with clinical benefit (94). In patients with acute myocardial infarction complicated by HF, levels of PINP and PIIINP rose (94). The administration of eplerenone, a specific aldosterone antagonist, was reported to have reduced elevated levels of PINP and PIIINP, findings associated with reductions in mortality and hospitalization for HF (95). These findings are examples of how biomarkers can be used to identify pathologic processes in patients with HF and thereby to help direct specific therapy (see Management section).

Inflammation. In 1956, the author participated in the description of the elevation of C-reactive protein (CRP), an inflammatory biomarker, in HF (96), an observation that has been confirmed and expanded on as assay methods have improved (97,98). The concentration of a number of pro-inflammatory cytokines, such as tumor necrosis factor-α and interleukin-6 (99) (Fig. 8), have also been reported to have been elevated in HF. In elderly subjects without HF, abnormal elevations in 3 inflammatory markers (CRP, tumor necrosis factor α, and interleukin-6) were reported to have been associated with a significant, 4-fold increase in the development of HF (98). The presence and levels of these biomarkers was correlated with the severity of HF; they appeared to have been independent predictors of outcome and to have provided important clues to the pathogenesis of HF. They could, in the future, become useful in testing novel antiinflammatory therapies in such patients.

Other biomarkers. ADRENOMEDULLIN. Adrenomedullin is a vasodilator peptide derived in part from the heart but also synthesized in vascular smooth muscle and endothelial cells (100). Because of its short half-life and instability, an assay for the MR sequence of its precursor (MR-proADM) has been developed and reported to be an independent predictor of mortality in ADHF (67,101) and of adverse outcomes in chronic HF (102) and stable CAD (68). While this marker has excellent sensitivity in detecting HF, its specificity has been questioned because of reported elevations in sepsis, glomerulonephritis, and chronic renal failure—perhaps not surprising given its synthesis in multiple tissues (102).

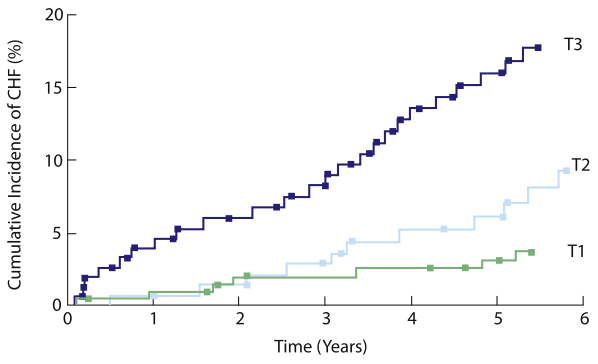

Figure 8 **Interleukin-6 and the Risk for Heart Failure**

Circulating interleukin-6, an inflammatory cytokine, was prospectively related to heart failure incidence in a continuous, graded fashion among participants in the Framingham Heart Study. CHF = congestive heart failure. T1, T2, and T3 represent the lowest, middle, and highest tertiles of concentration. Adapted with permission from Vasan RS, Sullivan LM, Roubenoff R, et al. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction. Circulation 2003;107:1486–91.

COPEPTIN. The concentration of circulating arginine vasopressin is elevated in patients with severe HF, but as is the case with ANP and adrenomedullin, its direct measurement is fraught with difficulties. Instead, copeptin, the C-terminal segment of pre-provasopressin, has been reported to be an excellent surrogate highly predictive of adverse outcomes in patients with ADHF (103) and chronic, stable CAD (68).

Biomarkers of renal failure. NEUTRAL GELATINASE-ASSOCIATED LIPOCALIN. Neutral gelatinase-associated lipocalin, a polypeptide marker of renal injury (104,105), is elevated in patients with ADHF and renal failure, that is, with the cardiorenal syndrome. Its elevation at the time of hospital discharge is a strong indicator of renal tubular damage and of adverse prognosis.

KIDNEY INJURY MOLECULE-1. Kidney injury molecule-1 is a glycoprotein expressed in the proximal tubule in renal injury and both its presence in patients with HF as well as its correlation with NT-proBNP suggest that renal involvement occurs in many patients with severe HF (106,107).

QUIESCIN Q6. The field of proteomics is likely to provide distinct "fingerprints" of circulating proteins in a variety of disorders, including HF (108). Just as genome-wide association studies (see Mechanisms section) represent an "unbiased" (i.e., not hypothesis-driven) search for genetic variants, liquid chromatography combined with mass spectroscopy has been used to carry out a search for plasma proteins in the proteome of patients with ADHF (109,110). This approach revealed that quiescin Q6 (QSOX1), a protein involved in the formation of disulfide bridges, was (along with BNP) associated with ADHF. After the discovery and isolation of QSOX1, its association with ADHF was validated in a second group of patients. Then, QSOX1 was reported to have been induced in the hearts of rats with HF following thoracic aortic constriction, lending credence to the specificity of this marker (109). The challenge now is to determine its biological significance and whether it provides information that could be useful to clinicians.

Multimarker strategies. There has recently been an interest in multimarker strategies to examine panels of biomarkers that assess different pathophysiologic pathways (Fig. 9) (60). An early study in patients with HFREF reported that a combination of proBNP, hsCRP, and myeloperoxidase (a marker of oxidative stress) provided greater predictive accuracy than did any of these markers individually (111). Subsequently, multimarker approaches to predict the risk for mortality in patients with ADHF (112–114), the

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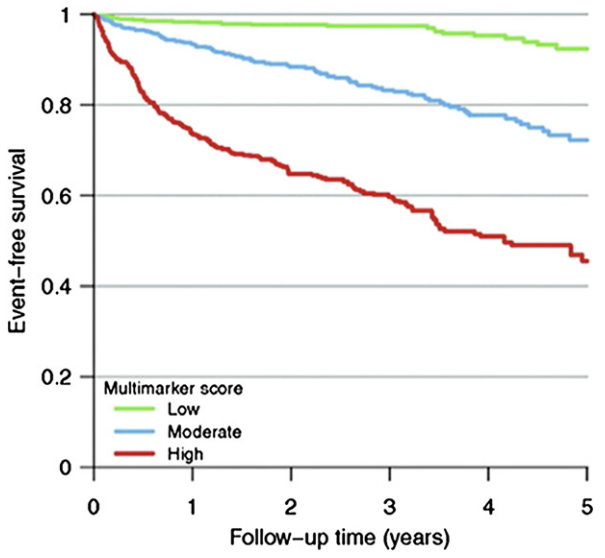

Figure 9 **Event-Free Survival According to Multimarker Score Category**

Kaplan-Meier curves illustrate the prevalences of all-cause death, cardiac transplantation, or left-ventricular assist device placement among Penn Heart Failure Study participants according to multimarker sore category tertiles ($p < 0.001$ by log-rank test). Reprinted with permission from: Ky B, French B, Levy WC, Sweitzer NK, et al. Multiple biomarkers for risk prediction in chronic heart failure. Circ Heart Fail 2012;5:183–90.

development of HF (115), and CVD-related death in community-based cohorts (116) have been described.

In a recent study of ambulatory patients with chronic HF, Ky et al. (77) tested the hypothesis that a group of 7 biomarkers, each reflecting a different pathophysiologic pathway in a manner analogous to those shown in Figure 7, could be combined into a multimarker score that would predict the risk for an adverse outcome, defined as death, cardiac transplantation, or placement of a ventricular-assist device. Each of these 7 biomarkers and their pathways were reported to have been independently associated with such an outcome. These biomarkers were BNP (neurohormonal activation), soluble fms-like tyrosine kinase receptor (vascular remodeling), hsCRP (inflammation), ST2 (myocyte stretch), cTnI (myocyte injury), uric acid (oxidative stress), and creatinine (renal function). The combined multimarker integer score provided an excellent assessment of risk (Fig. 9), with the hazard ratios of the intermediate- and higher-risk tertiles (adjusted for clinical risk) significantly elevated, to 3.5 and 6.8, respectively, compared to that of the lowest-risk tertile.

Management

During the last quarter of the 20th century, the treatment of chronic HFREF improved substantially with the development of 3 classes of drugs (ACE inhibitors/angiotensin II receptor blockers [ARBs], aldosterone antagonists, and β-adrenergic blockers), as well as internal cardioverter defibrillation and cardiac resynchronization therapy. These important developments came about largely as a consequence of years of preclinical and clinical research culminating in large-scale, multicenter clinical trials. The results of these trials are reflected in changes in the practice guidelines (18,117,118), which, in turn, have become standards of care expected by patients, physicians, and payers.

The therapeutic picture has been less favorable for HFPEF, in which, other than an emphasis on rigorous control of hypertension, rapid ventricular rate, and fluid retention, there is relatively little new that can be offered to the millions of patients with this disorder. However, 3 possible advances are under investigation. First, the phosphodiesterase-5 inhibitor sildenafil is being studied in a Phase II trial, RELAX (Phosphodiesterase-5 inhibition to improve clinical status and exercise capacity in diastolic heart failure) (119). Second, the Phase III TOPCAT (Aldosterone Antagonist Therapy in Adults with Preserved Ejection Fraction Congestive Heart Failure) trial (NCT00094302) has completed enrollment and is now in its follow-up phase (120). Third, the Phase II PARAMOUNT (Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction) trial is underway to investigate the effects of an angiotensin receptor neprilysin inhibitor, LCZ696, which combines in 1 molecule the ARB valsartan and the endopeptidase inhibitor that blocks the metabolism of the NPs. The latter action increases the generation of myocardial cyclic guanosine 3′,5′-monophosphate, which enhances myocardial relaxation and reduces ventricular hypertrophy. This dual blocker has been reported to have reduced NT-proBNP and left-atrial size to a significantly greater extent than valsartan alone in patients with HFPEF (121). This drug is currently undergoing a Phase III trial in patients with HFREF (PARADIGM-HF [Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure]).

In ADHF, the prevalence of death or readmission for HF within 6 months approaches 40% (122), and the currently available pharmacologic therapies have remained relatively unchanged during the past 3 decades. A string of Phase III trials in patients with ADHF have yielded largely negative results. Recent examples include PROTECT (Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline) (123), ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated HF) (124), and EVEREST (Effects of Oral Tolvaptan [a selective vasopressin 2 antagonist] in Patients Hospitalized for Worsening HF) (125), although the latter reported some improvement in dyspnea (126).

The management of ADHF requires rapid assessment and prompt treatment of any precipitating condition(s) (see Epidemiology section). Vasodilators (nitroglycerine, nitroprusside, or nesiritide) remain useful for hypertensive and normotensive patients, but hypotension must be carefully avoided in patients with ADHF. However, a number of other

vasodilators are being investigated. One compound, serelaxin, or recombinant human relaxin-2, is a naturally occurring peptide that is upregulated in normal pregnancy and that has undergone a positive phase II trial in patients with a normal or elevated blood pressure (127). In the RELAX-AHF trial, serelaxin or placebo was added to a regimen of standard therapy in 1,161 patients hospitalized with ADHF, evidence of congestion, and systolic pressure >125 mm Hg. Serelaxin was associated with improved dyspnea, less early worsening of HF, and greater early reductions in signs and symptoms of congestion. CVD-related mortality and all-cause mortality at 6 months (both exploratory endpoints) were each reduced. There were no significant reductions in CVD-related death or readmission for HF or renal failure (128). This agent is expected to undergo further study.

Positive inotropic agents. Impaired myocardial contractility represents a core problem in many patients with HF, both acute and chronic, and the search for tolerable and effective positive inotropic agents has gone on for decades. Drugs that increase the intracellular concentration of cyclic adenosine monophosphate, such as sympathomimetic amines and phosphodiesterase-3 inhibitors, are powerful positive inotropic agents whose activity results from an increase in cytoplasmic [Ca^{2+}]. This increase is accompanied by increases in myocardial oxygen demands, which lead to the development, exacerbation, or intensification of ischemia and/or life-threatening dysrhythmias. Although these agents typically improve hemodynamics and reduce symptoms of HF when infused intravenously for short periods (129,130), they often shorten survival (131).

MYOFILAMENT CA^{2+} SENSITIZERS. Attention is now focused on the development of inotropic agents that do not raise intracellular [Ca^{2+}] but instead increase myofilament sensitivity to Ca^{2+} (129). Levosimendan is a Ca^{2+} sensitizer with both inotropic and vasodilatory activity, the latter related to phosphodiesterase-3 inhibition (132,133). The guidelines for the treatment of HF published by the European Society of Cardiology recommend levosimendan in patients with symptomatic HFREF without hypotension (18). The vasodilatory activity of levosimendan makes it unsuitable in patients with hypotension. The effects of this drug on survival are not clear, and it is not available in the United States.

The small-molecule selective myosin activator mecamtiv mecarbil (134) raises stroke volume by prolonging the ejection period and increasing fractional shortening. Importantly, it does not elevate the velocity of shortening or of force development and therefore may not be "oxygen wasting," as are drugs that raise intracellular cyclic adenosine monophosphate. It has undergone Phase I and II testing and appears to be well-tolerated (in the absence of tachycardia) (135,136). Mecamtiv mecarbil is currently being studied in a 600-patient, Phase IIb trial (ATOMIC-AHF [Study to Evaluate the Safety and Efficacy of IV Infusion Treatment With Omecamtiv Mecarbil in Subjects With Left Ventricular Systolic Dysfunction Hospitalized for Acute Heart Failure]; NCT01300013). Other positive inotropic agents at earlier stages of development include SR33805, a potent Ca^{2+} channel blocker that also increases myofilament sensitivity to Ca^{2+} by inhibiting the activity of protein kinase A and by reducing the phosphorylation of cTnI (137).

An approach to enhancing myocardial contractility is to reduce the diastolic leak of Ca^{2+} from the SR via RyR2 (138,139) (see Mechanisms section). S100A1 is a protein that interacts with RyR2 and SERCA2a but requires administration by gene transfer (140). JTV519 (FKBP12.6), a 1,4-benzothiazepine, has been reported to have improved cardiac performance in experimental HF and in myocardium isolated from patients with HF (141,142). RyR2 stabilizers, termed rycals, are currently under development and have been reported to have reduced dysrhythmias and to have enhanced contractility in animal models (143). S107 is an orally available, more specific rycal (144). A number of positive inotropic agents that act on the SERCA2a/phospholamban system are also being investigated (145).

Pharmacologic treatment of chronic HF. Ivabradine is an inhibitor of the If current in the sinoatrial node (146) and thereby slows the heart rate. SHIFT (Systolic Heart Failure Treatment with Ivabradine Compared with Placebo Trial) (147) was conducted in patients with Class II or III HFREF, a heart rate >70 beats/min, and hospitalization for HF during the previous year. Ivabradine was associated with a significant reduction in the primary endpoint (CVD-related death or hospitalization for HF), driven by a decrease in hospitalization. Two-thirds of the patients were enrolled in eastern Europe and, with a few exceptions, did not receive internal cardioverter defibrillation or cardiac resynchronization therapy. Although the patients were appropriately treated with diuretics and ACE inhibitors (or ARBs), 40% did not receive a mineralocorticoid receptor antagonist. While 90% received β-blockers, only 26% were on full doses, and it has been questioned how effective ivabradine would have been in patients receiving robust, guideline-recommended therapy for HF (148). In the 2012 European Society of Cardiology guidelines for the treatment of HF (18), ivabradine was given a IIa/B indication.

Sildenafil is a selective inhibitor of phosphodiesterase-5A and is an effective pulmonary vasodilator. It has been reported to have improved exercise performance, exercise oxygen uptake (149), exercise capacity (150), and diastolic function (151) in patients with HFREF. In addition, sildenafil has been reported to have improved pulmonary and systemic hemodynamics in patients with severe aortic stenosis (152) and, as already mentioned, is currently being studied in HFPEF (119).

Cardiac progenitor/stem cell therapy. The observations that some cardiomyocyte renewal occurs normally in mammalian hearts (153,154) and accelerates following myocardial injury or infarction and in HF (155) have served as stimuli to studies on autologous cardiac stem/progenitor cell (CPC) therapy. A number of small- and moderate-scale trials of such therapy have focused on post–myocardial infarction patients and have employed autologous bone marrow–derived progenitor or stem cells.

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Jeevanantham et al. (156) reported a meta-analysis of 50 such studies involving 2,615 patients with ischemic heart disease—both early post-myocardial infarction and chronic CAD. Thirty-six of these were randomized controlled trials (n = 1,751) and 14 were cohort studies (n = 874). Although most of the individual studies failed to show significant benefit of treatment with autologous bone marrow-derived CPCs compared to standard therapy, most favored cell therapy numerically. Statistically significant benefits of cell therapy were achieved by pooling the results in the meta-analysis. Treatment with CPCs was associated with significant reductions in all-cause mortality and cardiac mortality, prevalence of recurrent myocardial infarction, infarct size, stent thrombosis, and LV end-systolic and end-diastolic volumes, while LVEF rose. Subgroup analysis revealed that the reductions in both end-systolic and end-diastolic volumes were significantly greater in patients with baseline EF <43% than in those with baseline EF >43%.

An alternative to autologous bone marrow–derived progenitor cells is autologous cardiac-derived stem cells. The results of 2 trials of therapy with such cells have been reported. In one, autologous c-kit–positive cells isolated from the atria obtained from patients undergoing coronary artery bypass grafting were cultured, processed, and reinfused (157,158). In the other, cardiosphere-derived cells grown from endomyocardial biopsy specimens were employed (159). Both trials were conducted in post–myocardial infarction patients with LV dysfunction, and the cells were administered by intracoronary infusion. In both trials, LV function was improved.

From the work carried out on cell therapy during the past decade, it appears that treatment with both autologous bone marrow-derived progenitor cells as well as cardiac-derived stem cells may be beneficial in the management of LV dysfunction in patients after acute myocardial infarction and in those with chronic ischemic heart disease. However, several important questions are raised by these observations: Because the studies were not blinded, was cotherapy comparable in control and cell-treated patients?; What is the preferred source of cells (bone marrow, cardiac, mesenchymal)?; How should they be processed?; and What is the optimum timing and route of administration? These and related questions can be answered only by adequately sized trials in which eligibility criteria; the nature and intensity of cotherapies; and the number, type, and pre-injection treatment of the cells are pre-specified. The first such large-scale (n = 3,000) trial, BAMI (Effect of Intracoronary Reinfusion of Bone Marrow-Derived Mononuclear Cells on All-Cause Mortality in Acute Myocardial Infarction; NCT01569178) has commenced in Europe. It seems likely that cell therapy will, within the next decade, occupy a significant place in the treatment of HF secondary to both acute and chronic ischemic heart disease. Its role in nonischemic HF is more difficult to predict.

Left ventricular assist devices. In 1994, the U.S. Food and Drug Administration approved the use of a pneumatically driven pulsatile-flow left ventricular assist device (LVAD) in critically ill patients as a bridge to cardiac transplantation. The technology evolved rapidly to an electrical device. The REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial reported that survival in patients with near-terminal HF who were not candidates for transplantation was prolonged by such a device, suggesting that chronic mechanical assistance could provide destination therapy (160). However, the available pulsatile-flow LVADs were large and required insertion of the pumping chamber within the peritoneal cavity or abdominal wall, and there were significant risks for infection; thrombosis; bleeding; perioperative death; and, later, device malfunction.

The development of nonpulsatile, continuous-flow LVADs represents a major step forward because these devices are smaller, have only a single moving part (the rotor), are more energy efficient, impose a lower perioperative mortality, and result in more favorable long-term survival than their more cumbersome predecessors (161). Although, with growing experience, thrombotic and hemorrhagic complications and device-related infections are diminishing (162), they have not been resolved (163), and long-term anticoagulation is still required. The increased shear stress associated with the use of the continuous-flow devices sometimes causes von Willebrand disease, resulting in excessive bleeding. Despite the great advantages of the continuous-flow devices compared to the pulsatile pumps, the former are associated with less mechanical unloading than the latter (164).

With the FDA-approved HeartMate II (Thoratec Corporation, Pleasanton, California) continuous-flow LVAD (161), the outcomes in patients with advanced HF eligible for cardiac transplantation have been reported to have been similar between patients who received an allograft or were treated with an LVAD and those who underwent destination therapy (165,166). The most recent report from INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) describes an annual growth rate of about 50% in the number of continuous-flow devices inserted during the past several years. Moreover, there has been a steady increase in the fraction of patients who receive such implants as destination therapy and therefore a reciprocal reduction in the fraction who receive implants inserted as a bridge to transplantation (167). The majority of patients who receive chronic LVAD support still have advanced HF and are inotrope dependent (167).

Two groups of critically ill patients still pose special challenges. They are in INTERMACS levels 1 or 2, in whom emergent LVAD implantation is required and in whom a 1-year survival of 65% has been reported (168). In critically ill patients who require biventricular support, a variety of devices have been employed. Survival at 6 months in 206 such patients was 56% (169). Although it may not be possible to carry out controlled trials in these 2 groups, based on historical controls, a much smaller percentage of patients

would have been expected to have survived before the current generation of devices became available.

Progress in the development of continuous-flow LVADs is continuing. The HeartWare LVAD (HeartWare International, Inc., Framingham, Massachusetts) is smaller than the HeartMate II. It is implanted directly into the left ventricle, is within the pericardial space, and has no mechanical bearings. The results of early trials have been encouraging (ADVANCE [Evaluation of the HeartWare Left Ventricular Assist Device for the Treatment of Advanced Heart Failure]; NCT00751972) (170).

Cardiac remodeling and recovery. A pleasant surprise has been the substantial reverse remodeling of the heart that occurs with chronic LVAD support (171,172). LV size and mass are reduced, EF rises, and there is regression of LV myocyte hypertrophy (173). Reductions in blood levels of catecholamines, renin, angiotensin II, arginine vasopressin, and tumor necrosis factor-α occur (174). Myocardial contractility is increased (175), as is the density of β-adrenergic receptors (176). Of great importance, Ca^{2+} cycling is improved (172), sarcolemmal Ca^{2+} entry is more rapid, and SR Ca^{2+} content and SERCA2a abundance are both increased (171).

It is important to distinguish the reverse remodeling changes summarized above, which are quite common in patients with advanced HF who have received long-term LVAD support, from myocardial recovery, in which patients can be successfully weaned from the device (177,178). The percentage of patients in whom sustained myocardial recovery has occurred varies widely among trials and has ranged from 1% to 40%. The lower response rates were seen most frequently in trials that did not systematically attempt weaning of patients from the device. The highest percentages came from 2 series of patients with advanced HF secondary to dilated cardiomyopathy from the Harefield hospital in Middlesex, England and the University of Louisville, Kentucky, an effort led by Birks and Yacoub (179,180). The long-term outcomes in the 40 patients who were bridged to recovery were comparable to those in patients who were bridged to transplantation (181). The Harefield protocol, which was begun when the device was implanted, involved an aggressive use of pharmacotherapy with high doses of an ACE inhibitor, ARB, carvedilol, and an aldosterone antagonist. When maximal regression of LV diameter occurred, carvedilol use was discontinued and replaced by clenbuterol, a β_2-adrenergic agonist that has been reported to induce physiologic hypertrophy in animal models (182). Echocardiographic changes following pre-explantation reduction of pump flow can be used to predict whether a patient will tolerate explantation (183). Confirmation of these salutary findings is awaited.

Gene therapy. The idea of replacing a faulty gene with a normal one has been a dream of biologists and clinical investigators for decades. However, the clinical application of gene transfer has faced a series of obstacles, forcing its suspension for about 2 decades. During this interval, extensive preclinical research has provided the theoretical infrastructure for this therapy, while effective and well-tolerated techniques have been developed. These efforts have paved the way for clinical trials of gene therapy. Advanced HF is the first major CVD in which gene transfer is being studied.

A variety of viral vectors (carriers of the gene that is transferred) have been explored, with adeno-associated viruses appearing to be optimal because they are nonpathogenic and exhibit low immunogenicity (184). After administration, the vector of the gene binds to a receptor on the target cell—the cardiomyocyte in the case of HF—undergoes endocytosis; traverses the cytoplasm; and penetrates the nucleus, where the gene is incorporated into the genome and transcription occurs (Fig. 10).

Several methods of gene delivery have been employed, including coronary artery infusion, direct intramyocardial injection, retrograde coronary venous infusion, and injection into the pericardial space (184). A number of molecular targets are under investigation in animal models, including β_2-adrenergic receptors (185), inhibitors of G protein–coupled receptor kinase, and a variety of Ca^{2+} cycling proteins (see Mechanisms section). The latter include S100A, a Ca^{2+} modulating protein (140), as well as an inhibitor of phospholamban (186). Furthest along in clinical trials is SERCA2a, which reloads SR with Ca^{2+} during diastole (40) (see Mechanisms section) and has been reported to be deficient in patients with HF. After extensive preclinical studies (187) and a Phase I trial in patients with HF that demonstrated tolerability, a Phase II randomized, double-blind, placebo-controlled trial, CUPID (Efficacy and Safety Study of Genetically Targeted Enzyme Replacement Therapy for Advanced Heart Failure; NCT00454818) (188), was conducted. The coronary arterial infusion of adeno-associated virus type 1 carrying the gene for SERCA2a resulted in reverse remodeling, a reduction in circulating NPs, and symptomatic improvement, and this experimental treatment was well tolerated.

Other gene therapies for HF being investigated include the use of adenovirus-5 virus as the vector of the gene for human adenyl cyclase 6. Another therapy involves the administration of the "naked" gene for stromal-derived factor 1 by direct myocardial injection; stromal-derived factor 1 enhances myocardial repair by improving the "homing" of stem cells to the site of tissue injury (184).

The possibility of treating HF by gene transfer is not limited to delivering the gene to the myocardium directly (189). There is evidence that CPCs that are treated to overexpress Akt (190) and Pim-1, a prosurvival and proproliferation kinase (191), increase long-term cell survival and enhance myocardial regeneration in mice. If this approach were developed further, it has the potential to increase enormously the benefits that can be achieved from treatment with autologous CPCs.

Future Directions

Demographic realities are leading to an inescapable conclusion: If the incidence of new cases of HF were to remain at the present level of 1% per year in persons age >65 years, with the expected aging of the population, by 2050

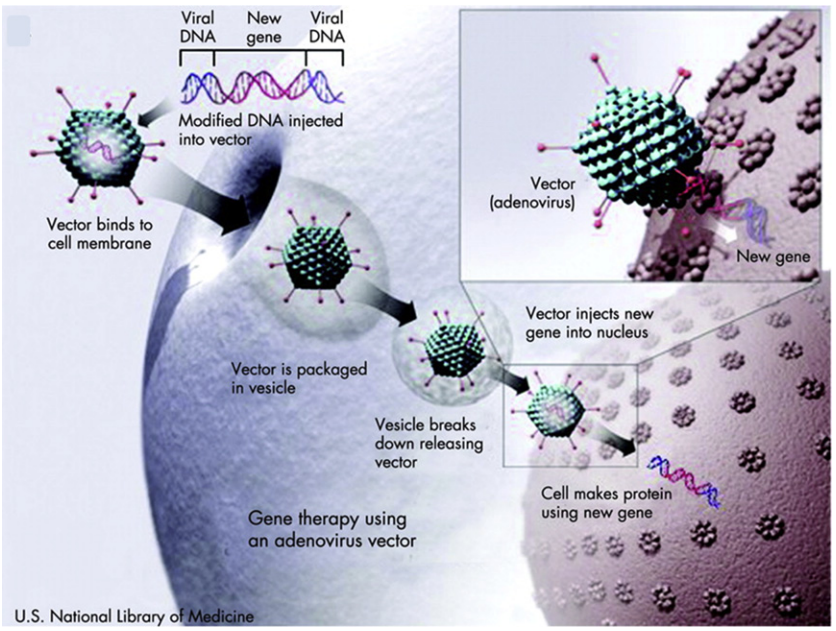

Figure 10 Gene Transfer

Viral vectors bind to cell surface receptors, initiating endocytosis. Once internalized, the viral particles avoid degradation and travel to "dock" on the nuclear envelope membrane pores, and the genome is delivered into the cell nucleus. Created by the U.S. National Library of Medicine. Reprinted with permission from Lyon AR, Sato M, Hajjar RJ, Samulski RJ, Harding SE. Gene therapy targeting the myocardium. Heart 2008;94:89–99.

there would be >1 million new cases per year in the United States. While the war to reduce the toll of CVD, broadly considered, must continue, the battle to control HF has now moved to the center stage of this war. This battle will be long and difficult, and because the "enemy has many faces," it will have to be fought simultaneously on multiple fronts and with many different weapons.

Prevention. In 2001, the authors of the American College of Cardiology/American Heart Association guidelines for the treatment of HF (192) were prescient when they defined the first stage of HF (stage A) as occurring in patients who have no symptoms of HF and no structural disease of the heart, but who are at high risk for HF. In so doing, they emphasized the importance of preventing HF long before it becomes apparent clinically. A wide variety of approaches to the prevention of CVD are now available. They begin with education and setting goals for lifestyle changes (193).

Perhaps most important is the prevention of the disorders that give rise to HF in the first place. Measures for the primary prevention of CAD, the most common cause of HF in industrialized nations, are well established, but they are not applied with sufficient vigor and consistency. Of course, it remains of critical importance to reduce CVD risk factors such as elevated cholesterol and blood pressure once they develop. However, because these risk factors may begin to exert their effects long before they are clinically apparent, interventions should commence earlier to prevent their development, an approach referred to as primordial prevention. To accomplish this, it may be desirable to intervene in childhood or adolescence in 2 populations. The first is those with genomic profiles associated with the risk for hypercholesterolemia and coronary arterial calcifications (194) and who have additional risk factors, such as diabetes and hypertension, as the genomics of these conditions become better defined. The second group is children and adolescents who are in the top quartiles of their age and sex in levels of cholesterol and blood pressure. Because these rankings usually track into adulthood, aggressive management of these two risk factors should be begun as early as possible, perhaps in the second decade of life.

There are 2 additional groups of asymptomatic individuals in whom the risk for HF is elevated. These include ostensibly healthy persons with elevated biomarkers such as NT-proBNP (71) and cardiac-specific hsTn (89,90). Screening for these and subsequent biomarkers discovered by evolving proteomic techniques (108–110) should become routine and begun in early adulthood. The second group is individuals who have exhibited structural disorders of the heart, but without overt clinical manifestations of HF, that is, stage B in the American College of Cardiology/American Heart Association classification (192). For these latter 2 groups, modern sensitive imaging techniques (preferably those that do not require radiation) can be of enormous value because they can identify persons in whom very intensive prevention of HF is mandatory and allow the assessment of the progression, halting, and possibly regression of structural changes that are the forerunners of clinical HF.

In patients with symptomatic HF (stage C [192]), a battery of biomarkers such as those shown in Figure 7 and employed successfully by Ky et al. (77) (Fig. 9) will be useful. It is likely that such multimarker panels will be expanded as the various pathobiological causes of HF become better understood. When such multimarker approaches are combined with genomics and advanced imaging (110), the resultant profiles are likely to aid in the selection of personalized therapy, and by remeasuring the biomarkers at regular intervals, the effectiveness of therapy can be evaluated.

Treatment. Insofar as the treatment of overt HF is concerned, as discussed in the section on pharmacologic management, drugs tailored to prevent or reverse the specific molecular abnormalities present in the various types and stages of HF are in active development. Patient education is of critical importance to prevention, as already mentioned, but it must be carried out in patients with overt HF as well. Because most patients with HF are elderly and likely require many medications, their adherence to HF therapies is often suboptimal (195). Also, it is increasingly appreciated that there are genetic variations in responses to drugs commonly used in the treatment of HF, including diuretics, neurohormonal antagonists, β-blockers, and ACE inhibitors (196). There is growing interest in the pharmacogenetic targeting of drugs for the treatment of HF (197,198). It is anticipated that when genetic differences in responses to drugs are taken into account, the efficacy–tolerability relation will improve and contribute to the personalized treatment of patients with HF. An illustrative example of this approach comes from a study of a variant in the gene that encodes the enzyme G-protein coupled receptor kinase 5, which downregulates β-adrenergic receptors. A single amino acid substitution of this enzyme results in what has been termed "genetic β-blockade" (198,199). Patients with HF who were carriers of this single-nucleotide polymorphism exhibited improved survival.

The use of additional drugs in the experimental stage (see Management section) is expected to become routine in the treatment of HF. Gene therapy will be applied in patients in whom pharmacotherapy has not halted the progression of HF. Like pharmacotherapy, gene therapy will be individualized to target patient-specific molecular abnormalities involved in HF.

Cell death that is localized, as in myocardial infarction, or generalized, as in a variety of cardiomyopathies as well as in chronic hypertension, is the direct cause of HF in many patients. Therapy with autologous progenitor or stem cells is likely to play a progressively more important role in the management of patients in whom a substantial loss of myocytes has occurred and who are therefore at a high risk for, or who have already developed, overt HF. The possibility of transferring genes that enhance the survival of autologous progenitor cells could represent a "happy marriage" of the 2 techniques (190,191) and be mutually reinforcing in the treatment of HF.

Advanced HF. We are currently in the midst of a rapid evolution in the management of advanced HF that is reminiscent of the enormous progress made in the treatment of chronic, moderately severe HFREF in the 1980s and 1990s. The prolonged survival and the improvement in the quality of life in patients with advanced HF by the use of chronic LVAD support are leading to a "sea change" in the management of these gravely ill patients.

Until a few years ago, such patients either died or, if candidates for cardiac transplantation, were hospitalized, sometimes for many months, while on inotropic support, before a donor heart became available; many did not survive this waiting period. With the advent of continuous-flow LVADs, such support is now begun in some of these patients as soon as they are listed for transplantation, to reduce the risk for death and to maintain quality of life during the waiting period. As LVADs continue to improve, as the mortality and complications associated with their implantation decline further, both the absolute number and the fraction of patients who receive these devices as destination therapy, as opposed to as a bridge to transplantation, will continue to rise. Hopefully, with increasing use, the cost of the devices, the duration of the hospitalization required for implantation, and the need for subsequent rehospitalizations for HF or complications of the device will all decline, and making this approach more cost-effective.

Perhaps even more remarkable is how the aforementioned observations on cardiac reverse remodeling and, in a few selected instances, actual myocardial recovery (see Management section), are altering the concepts of HF. Until recently, advanced HF was generally considered to be an irreversible, end-stage condition. Gross examination of the hearts of patients dying from HF and examined at autopsy, or those removed from transplant recipients, usually revealed flabby, dilated, scarred organs. Histologically, they showed hypertrophied muscle bundles, often fragmented and in disarray, with excessive fibrous tissue; when viewed on electron microscopy, the myocytes were misshapen, with disturbed intracellular structures. From such inspection, it seemed unlikely that such damaged organs could ever resume successful support of the circulation. However, it is now apparent that, just as a fractured bone can heal after it has been properly treated and immobilized, so can a failing heart exhibit substantial reverse remodeling if it can be "rested" by long-term LVAD support. In some patients with dilated cardiomyopathy (179–182), the native heart can resume its function, thereby allowing explantation of the LVAD. These observations, if confirmed, would constitute a paradigm shift, with profound implications. They would suggest that LVAD support can be commenced earlier in the course of HF, with the goal of using LVAD support as a bridge to recovery.

An important step would be the extension of this approach from patients with dilated cardiomyopathy, in some of whom cardiac recovery after LVAD support has been demonstrated, to those with ischemic cardiomyopathy, a much more common condition. Such a goal would be greatly facilitated by the next generation of LVADs, which will be totally implantable and will not require a transcutaneous line. It is

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now possible to envision a time when treatment with long-term LVAD support might be extended from patients in New York Heart Association functional class IV to the many, many more patients who remain in class III despite aggressive treatment (including the use of drugs still in the developmental stage, as well as gene and cell therapy and their combination). These patients would receive LVAD support until myocardial recovery has been achieved, at which time the device might be safely explanted.

Conclusions

Substantial improvements in the prevention and management of HF present formidable challenges, but these challenges may be met because much of the necessary groundwork has already been carried out. The pages of *JACC: Heart Failure* are expected to report the important skirmishes and victories of this last great battle in the war on CVD. In so doing, *JACC: Heart Failure* will accelerate the translation of scientific discoveries and technical developments to clinical care, will help to educate health care professionals, and will thereby make an important contribution to improving quality and duration of life in patients worldwide.

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