Despite repeated attempts to develop a unifying hypothesis that explains the clinical syndrome of heart failure, no single conceptual paradigm for heart failure has withstood the test of time. One logical explanation for our inability to define the syndrome of heart failure in precise mechanistic and/or clinical terms is that the clinical syndrome of heart failure almost certainly represents the summation of multiple anatomic, functional, and biological alterations that interact together in an exceedingly complex manner and in different genetic and environmental backgrounds over a sustained (but variable) period of time. Thus, it is not surprising that clinicians and investigators have used a variety of increasingly complex model systems in an attempt to describe the syndrome of heart failure. Whereas clinicians initially viewed heart failure as a problem of excessive salt and water retention that was caused by abnormalities of renal blood flow (the “cardiorenal model”), as physicians began to perform careful hemodynamic measurements, it also became apparent that heart failure was associated with a reduced cardiac output and excessive peripheral vasoconstriction. This latter realization led to the development of the cardio-circulatory or hemodynamic model for heart failure, wherein heart failure was thought to arise largely as a result of abnormalities of the pumping capacity of the heart and excessive peripheral vasoconstriction. However, although both the cardiorenal and cardio-circulatory models for heart failure explained the excessive salt and water retention that heart failure patients experience, neither of these models explained the relentless disease progression that occurs in this syndrome. That is, although the cardiorenal models provided the rational basis for the use of diuretics to control the volume status of patients with heart failure, and the cardio-circulatory model provided the rational basis for the use of inotropes and intravenous vasodilators to augment cardiac output, these therapeutic strategies have not prevented heart failure from progressing, nor have they led to prolonged life for patients with moderate to severe heart failure.

On the basis of the above arguments, it has become increasingly apparent that heart failure can no longer be defined in simple hemodynamic terms. Indeed, what has become increasingly apparent is that at some point in time in the overall pathogenesis of heart failure, the disease will progress independently of the patient’s hemodynamic status. Accordingly, the currently accepted working definition that “heart failure occurs when an abnormality of cardiac function causes the heart to fail to pump blood at a rate required by the metabolizing tissues or when the heart can do so only with an elevated pressure,” will likely prove to be only partially correct. Indeed, the clinical observation that heart failure can progress independently of the hemodynamic status of the patient has focused interest on the potential spectrum of mechanism(s) responsible for disease progression in the failing heart.

Figure 1 provides a general conceptual framework for discussing the development and progression of heart failure. As shown, heart failure may be viewed as a progressive disorder that is initiated after an index event either damages the heart muscle, with a resultant loss of functioning cardiac myocytes, or alternatively disrupts the ability of the myocardium to generate force, thereby preventing the heart from contracting normally. This index event may have an abrupt onset, as in the case of a myocardial infarction, it may have a gradual or insidious onset, as in the case hemodynamic pressure or volume overloading, or it may be hereditary, as in the case of many of the genetic cardiomyopathies. Regardless of the nature of the inciting event, the feature that is common to each of these index events is that they all, in some manner, produce a decline in pumping capacity of the heart. In most instances, patients will remain asymptomatic or minimally symptomatic following the initial decline in pumping capacity of the heart, or will develop symptoms only after the dysfunction has been present for some time. Thus, when viewed within this conceptual framework, left ventricular (LV) dysfunction is necessary but not sufficient for the development of the syndrome of heart failure.

Although the precise reasons why patients with LV dysfunction remain asymptomatic is not certain, one potential explanation is that many compensatory mechanisms become activated in the setting of cardiac injury or depressed cardiac output appear to be able to sustain and modulate LV function.
Heart Failure as a Progressive Model

**Neurohormonal Mechanisms**

It has been suggested that heart failure should be viewed as a neurohormonal model, in which heart failure progresses as a result of the overexpression of biologically active molecules that are capable of exerting toxic effects on the heart and circulation. Thus far, a variety of proteins including norepinephrine, angiotensin II, endothelin, aldosterone, and tumor necrosis factor (TNF) have been implicated as some of the potentially biologically active molecules whose biochemical properties are sufficient to contribute to disease progression in the failing heart. It bears emphasis that the term neurohormone is largely an historical term, reflecting the original observation that many of the molecules that were elaborated in heart failure were produced by the neuroendocrine system and thus acted on the heart in an endocrine manner. However, it has since become apparent that a great many of the so-called classic neurohormones such as norepinephrine and angiotensin II are synthesized directly within the myocardium, and thus act in an autocrine and paracrine manner. Furthermore, molecules such as angiotensin II, endothelin, and TNF are peptide growth factors and/or cytokines produced by a variety of nucleated cell types within the heart, including cardiac myocytes, and thus do not necessarily have a neuroendocrine origin. Nonetheless, the important unifying concept that arises from the neurohormonal model is that the overexpression of portfolios of biologically active molecules can contribute to disease progression independently of the hemodynamic status of the patient, by virtue of the direct toxic effects that these molecules exert on the heart and circulation. The evidence in support of this point of view is derived from 2 lines of investigation. First, many experimental models which have shown that pathophysiologically relevant concentrations of neurohormones are sufficient to mimic some aspects of the heart failure phenotype. Second, clinical studies have shown that antagonizing neurohormones leads to clinical improvement for patients with heart failure. Thus, one logical explanation for why heart failure progresses is that long-term activation of a variety of neurohormonal mechanisms produces direct end-organ damage within the heart and circulation. Accordingly, progressive activation of neurohormonal mechanisms may explain why heart failure may develop insidiously many years after an acute myocardial infarction, despite the absence of ongoing ischemia. The neurohormonal model also explains why the so-called heart failure phenotype appears remarkably consistent in patients with different etiologies for their heart failure, insofar as disease progression is ultimately driven by very similar portfolios of biologically active molecules, regardless of the inciting cause.

**Is the Neurohormonal Model Adequate to Explain the Progression of Heart Failure?**

Despite the many strengths of the neurohormonal model in terms of explaining disease progression and the many insights for a period of days to months to years. The portfolio of compensatory mechanisms that have been described include early activation of the sympathetic nervous system and salt and water retaining systems in order to preserve cardiac output as well as activation of a family of vasodilatory molecules, including natriuretic peptides, prostaglandins (PGE₂ and PGE₁), and nitric oxide. However, it bears emphasis that our understanding of the family of molecules that may be involved in this process is far from complete. Moreover, we have very little information with respect to how genetic background, gender, age, or environment impact these compensatory mechanisms.

As shown in Figure 1, the compensatory mechanisms activated following the initial decline in the pumping capacity of the heart are able to modulate LV function within a physiological/homeostatic range, such that the functional capacity of the patient is preserved or is depressed only minimally. Thus, patients may remain asymptomatic or minimally symptomatic for a period of years. However, at some point in time patients will become overtly symptomatic, with a resultant striking increase in morbidity and mortality. Why this transition to symptomatic heart failure occurs, and exactly how this transition occurs, and whether it occurs in all patients with LV dysfunction remains unknown and represents an important area of discovery in heart failure. What is known, however, is that the transition to symptomatic heart failure is accompanied by further activation of neurohormonal and cytokine systems, as well as a series of adaptive changes within the myocardium, collectively referred to as LV remodeling. Although there are further modest declines in the overall pumping capacity of the heart during the transition to symptomatic heart failure, the weight of experimental and clinical evidence suggests that heart failure progresses occur independently of the hemodynamic status of the patient. Accordingly, it becomes difficult to ascribe the transition to symptomatic heart failure to worsening LV function alone. Thus, one important question that arises from the above discussion is why heart failure progresses.
that neurohormonal models have provided in terms of drug development for heart failure, there is increasing clinical evidence to suggest that our current neurohormonal models fail to completely explain disease progression in heart failure. This concept is illustrated by the differences in the Kaplan-Meier curves observed in lipid lowering trials for patients with coronary artery disease and for neurohormonal antagonism for patients with heart failure. Figure 2A illustrates a Kaplan-Meier curve for death or nonfatal myocardial infarction for patients who were randomized to receive placebo or pravastatin in the West of Scotland Coronary Prevention Study.20 As shown, the Kaplan-Meier curves begin to diverge at 1 year and then continue to diverge over the next 5 years. The observation that the event curves continue to diverge over time implies that pravastatin has in some way altered the underlying mechanism of the disease process, presumably through lipid lowering. In contrast, Figure 2B illustrates Kaplan-Meier curves for death or hospitalization for heart failure for patients who were randomized to placebo or enalapril in the treatment arm of the Studies on Left Ventricular Dysfunction (SOLVD).16 As shown, the curves begin to diverge at 6 months, suggesting that enalapril has at least initially altered the underlying mechanism of the disease process, presumably by preventing disease progression. However, as shown in Figure 2B, the Kaplan-Meier curves for the placebo and enalapril arms become parallel between 18 and 48 months. Interestingly, similar patterns can be observed in the Kaplan-Meier curves for the patients who are randomized to receive both $\beta$-blockers and ACE inhibitors.19 The observation that the event curves become parallel following neurohormonal antagonism suggests that there may be an attenuation or loss of effectiveness of neurohormonal antagonism as heart failure progresses.

Although the precise mechanism(s) for this attenuation or loss of effectiveness of neurohormonal antagonism is not known, there are at least 4 potential explanations that warrant a brief discussion. One obvious explanation is that it may not be possible to achieve complete inhibition of the renin angiotensin system or the adrenergic system in heart failure because of dose-limiting side effects of ACE inhibitors and $\beta$-blockers. A second explanation is that there may be alternative metabolic pathways for neurohormones that are not antagonized by conventional treatment strategies. For example, angiotensin converting enzyme inhibitors do not antagonize the conversion of angiotensin I to angiotensin II within the myocardium by tissue chymase.21,22 Therefore, ACE inhibitors do not completely antagonize the renin angiotensin system. Third, the currently available portfolio of neurohormonal antagonists, namely ACE inhibitors and $\beta$-blockers, may not antagonize all of the biologically active systems that become activated in the setting of heart failure (eg, endothelin, aldosterone, and TNF). Indeed, given the inherent biological redundancy of all mammalian systems, it is perhaps predictable that there will be many biologically active molecules that are sufficient to contribute to disease progression by virtue of their toxic effects on the heart and the circulation. Thus, it is likely that with the current technologies for gene expression monitoring, as well as the innovative cloning strategies that are being used, it is only a matter of time before investigators identify new families/classes of biologically active molecules capable of contributing to disease progression. A fourth, albeit speculative explanation for the loss of effectiveness of neurohormonal antagonism is that at some point in time, heart failure may progress independently of the neurohormonal status of the patient. Thus, analogous to the limitations described for hemodynamic models for heart failure, neurohormonal models may be necessary but not sufficient to explain all aspects of disease progression in the failing heart.

**LV Remodeling: Cause or Consequence of Heart Failure?**

Natural history studies have shown that progressive LV remodeling is directly related to future deterioration in LV performance and a less favorable clinical course in patients with heart failure.23–25 Although some investigators currently view LV remodeling simply as the end-organ response that occurs following years of exposure to the toxic effects of long-term neurohormonal stimulation, others have suggested that LV remodeling may contribute independently to the progression of heart failure.23 Given the potential central importance of LV remodeling in the progression of heart failure, the following section will focus on the basic cellular and molecular mechanisms responsible for this process.

In the context of the present discussion, the term LV remodeling refers to the changes in LV chamber and volume not related to preload mediated increases in sarcomere length.23,26 Although the complex changes that occur in the heart during LV remodeling have canonically been described in anatomic terms, the process of LV remodeling also impacts importantly on the biology of the cardiac myocyte, on changes in the volume of myocyte and nonmyocyte components of the myocardium, as well as on the geometry and architecture of the LV chamber (Table 1). Whereas each of
These various components of the remodeling process may contribute importantly to the overall development and progression of heart failure, it is extremely unlikely that any single aspect of the remodeling process itself will satisfactorily explain the progressive cardiac decompensation that occurs as heart failure advances. Accordingly, the remaining discussion will focus on the collective changes that occur in the cardiac myocyte, the myocardium, and the LV chamber, with an emphasis on those aspects of the remodeling process that might potentially contribute to disease progression.

### Alterations in the Biology of the Cardiac Myocyte

Numerous studies have suggested that failing human cardiac myocytes undergo several important changes that might be expected to lead to a progressive loss of contractile function, including decreased α-myosin heavy chain gene expression with a concomitant increase in β-myosin heavy chain expression,27 progressive loss of myofilaments in cardiac myocytes,28 alterations in cytoskeletal proteins,28 alterations in excitation contraction coupling,29 as well as desensitization of β-adrenergic signaling.30 Although many of the aforementioned changes may be thought of as beneficial in terms of protecting myocytes against the potential deleterious consequences of excessive neurohormonal activation, collectively these changes would be expected to lead to a defect in myocyte contractile function as well as decreased loss of responsiveness to normal adrenergic control mechanisms, both of which are hallmarks of failing human myocardium. And indeed, when the contractile performance of isolated failing human myocytes has been examined under very simple experimental conditions, investigators have found that there is an ≈50% decrease in cell shortening in failing human cardiac myocytes when compared with nonfailing human myocytes.31 Moreover, as noted in the above discussion, this defect in cell shortening has several important components which may act combinatorially to produce the observed phenotype of cellular contractile dysfunction. Thus, the contractile dysfunction that develops within myocytes during the process of LV remodeling is likely to involve ensembles of genes, including those that regulate calcium handling, sarcoplasmic reticulum, β-adrenergic signaling, and the cytoskeleton, all of which may interact in an exceedingly complex manner within the cardiac myocyte to produce contractile dysfunction.

### Are the Defects in Myocyte Function Reversible?

The experimental literature suggests that alterations in the biology and the contractility of the failing cardiac myocyte are reversible following β-adrenergic blockade.32 Although the mechanism for the improved contractile performance in isolated myocytes is not known, the improvement in myocyte contractility has been linked to an increase in the density of myofilaments within the failing myocytes. Thus, in this experimental model, β-adrenergic blockade appeared to be able to reverse some of the deleterious alterations in the biology of the myocyte. Whether the improvement in LV ejection fraction that occurs in heart failure patients placed on β-adrenergic blocking agents33 is the result of the reversal on unfavorable alterations in the biology of the adult myocyte remains speculative for the present, but it is an attractive explanation.7 Another example of the potential reversibility of myocyte contractile defects is suggested by the studies in which isolated failing myocytes obtained from hearts that had been supported with a LV assist device manifested improved shortening and responsiveness to isoproterenol when compared with myocytes isolated from hearts that had not been supported with a LV assist device.34 Although this interesting study did not directly demonstrate an improvement in myocyte function, it does suggest that defects at the myocyte level are potentially reversible.

### Alterations in Failing Myocardium

The unfavorable alterations that occur in failing myocardium may be categorized broadly into those that occur in the volume of cardiac myocytes and changes that occur in the volume and composition of the extracellular matrix. With respect to the changes that occur in cardiac myocyte component of the myocardium, there is increasing evidence to suggest that progressive myocyte loss, through both necrotic and apoptotic cell death, may contribute to progressive cardiac dysfunction and LV remodeling. For example, it has long been postulated that excessive adrenergic drive might be overtly deleterious by triggering myocyte necrosis.35 Indeed, concentrations of norepinephrine available within myocardial tissue, as well as in circulating levels in patients with advanced heart failure, are sufficient to provoke myocyte necrosis in experimental model systems.13 Moreover, excessive stimulation with either angiotensin II or endothelin has been shown to provoke myocyte necrosis in experimental models.12 Until recently, the clinical evidence which suggested that myonecrosis occurred in heart failure was confined to histological specimens of myocardium obtained during implantation of LV assist devices, which revealed the presence of contraction band necrosis. However, additional evidence for the existence of ongoing myonecrosis in patients...
with heart failure is suggested by a recent study that showed that levels of circulating troponin I were increased 3- to 4-fold in patients with advanced heart failure.36 Taken together, these clinical studies suggest that myocyte necrosis may contribute to the progressive myocardial remodeling and LV dysfunction that occurs as heart failure progresses.

The relatively recent recognition that mammalian cells are capable of undergoing apoptosis, or programmed cell death, has prompted the intriguing thought that heart failure might also progress by virtue of progressive apoptotic cell death. This point of view has received increasing support with the recognition that DNA damage characteristic of apoptotic cell death occurs in myocytes from failing hearts.37,38 Moreover, many of the factors that have been implicated in the pathogenesis of heart failure, including myocardial stretch, norepinephrine, TNF, oxidative stress, and angiotensin II, have been shown to trigger apoptosis in a variety of simple in vitro and vivo experimental model systems.39–41 Nonetheless, despite the undeniable intrinsic appeal of programmed cell death as a potentially important mechanism for disease progression in the failing heart, there are several caveats that warrant discussion. First, all of the currently available assessments of myocyte apoptosis in failing hearts have been performed in explanted hearts obtained from patients awaiting cardiac transplantation, many of whom were receiving intransvenous inotropic support before cardiac transplantation. Given that catecholamines can provoke apoptosis in experimental models,42 the existing clinical studies may overestimate the true frequency of apoptosis in the failing heart.37,38 Second, at present, there are no data with respect to whether myocyte apoptosis occurs in patients with mild to moderate heart failure. Thus, it is not clear whether apoptosis contributes to disease progression in heart failure, or whether instead it is a phenomenon that is observed only in end-stage heart failure. Third, the current estimates of myocyte apoptosis in failing myocardium range from clinically insignificant levels of 0.003%/y (estimated myocytes cell loss =1%/y; [Jutta Schaper, personal oral communication, June 24, 1998]) to clinically unrealistic estimates of =5% to 35% (estimated myocyte loss >100%/y). These striking disparities make it difficult to know exactly what contribution apoptosis plays in progressive cardiac dysfunction. Thus, although the general concept that myocyte cell loss may contribute to the progressive myocardial dysfunction and myocardial remodeling is likely to have validity, further clinical studies will be necessary to determine the frequency of necrosis and apoptosis in patients with mild to moderate heart failure. These studies will be needed in order to obtain a clearer understanding of whether cell death occurs early and continually in heart failure or, instead, only in end-stage hearts.

In addition to alterations in the volume and composition of the cardiac myocytes, there are several important changes that also occur within the extracellular matrix component of the myocardium.43–46 Perhaps the most widely recognized alteration that occurs in the extracellular matrix is the development of perivascular fibrosis around intramyocardial blood vessels, as well as replacement fibrosis, which is the term that has been used to describe the excessive deposition of fibrillar collagen that occurs following the death of myocytes. Enthusiasm for the idea that progressive fibrosis plays an important role in the progression of heart failure has been engendered by experimental studies; these studies have shown that angiotensin II, endothelin, and aldosterone47–49 are sufficient to trigger excessive fibrosis in myocardial tissue, thus providing a potential biochemical explanation for the development of the excessive fibrosis in heart failure.

Although excessive fibrin deposition has been invoked as one logical explanation to explain the progressive contractile dysfunction that occurs in the failing heart, until recently it has been difficult to explain precisely how excessive fibrosis (which would be expected to lead to stiffer and less compliant ventricle) could explain the progressive LV dilation that occurs during the process of LV remodeling. Recently, it has been suggested that a family of collagenolytic enzymes become activated within the failing myocardium.43,44,46 Collectively these collagenolytic enzymes have been referred to as matrix metalloproteinases (MMPs). Conceptually, progressive activation of MMPs might be expected to lead to progressive degradation of the extracellular matrix, which in turn lead to mural realignment (slippage) of myocyte bundles and/or individual myocytes within the LV wall, and thus account for the LV wall thinning and the dilation that occurs in heart failure. Although the precise biochemical triggers responsible for activation of MMPs are not known, it bears emphasis that TNF, as well as other cytokines and peptide growth factors expressed within the failing myocardium, are capable of activating MMPs. However, the biology of matrix remodeling in heart failure is likely to be much more complex than the simple presence or absence of MMP activation, insofar as degradation of the matrix is also controlled by glycoproteins termed tissue inhibitors of matrix metalloproteinases (TIMPs), capable of regulating the activation of MMPs by binding to and preventing these enzymes from degrading the collagen matrix of the heart. However, the exact role of TIMPs in the failing heart is far from clear, in that it appears that under certain conditions TIMPs may actually stabilize and/or localize MMPs, which in turn may facilitate the activation of MMPs. When viewed together, the above observations suggest that the alterations in the extracellular matrix that occur during LV remodeling are likely to be far more complex than were proposed originally, and that there may be periods of ongoing fibrin degradation and deposition throughout the process of LV remodeling.

**Are the Defects in the Failing Myocardium Reversible?**

In contrast to the defects that occur in the failing myocyte, many of the defects that occur within the myocardium, most notably those affecting myocyte survival, are not reversible and may therefore directly contribute to disease progression. Furthermore, whereas changes in the extracellular matrix may be partially reversible in some situations,50–52 there is no current clinical evidence to suggest that the magnitude of the fibrotic changes that occur in the myocardium are completely reversible. Thus, defects that arise at the myocardial level represent an important and potentially irreversible mechanism for disease progressive.

**Alterations in Ventricular Chamber Geometry**

On the basis of the above discussion, it is clear that the changes that occur in the biology of the failing myocyte and...
TABLE 2. Mechanical Disadvantages Created by LV Remodeling

- Increased wall stress (afterload)
- Afterload mismatch
- Episodic subendocardial hypoperfusion
- Increased oxygen utilization
- Sustained hemodynamic overloading
- Worsening activation of compensatory mechanisms

in the biology of failing myocardium contribute to the development of the LV dilation and LV dysfunction that occur during the process of LV remodeling. The importance of this statement is that there are several lines of evidence to suggest that the deleterious changes that occur in the geometry of the remodeled LV may promote worsening heart failure. One of the first observations with respect to the abnormal geometry of remodeled ventricle was the consistent finding that the remodeled heart was not only larger but was also more spherical shape. As shown in Table 2, the increase in LV size and resultant change in LV geometry from the normal prolate ellipse to a more spherical shape creates several de novo mechanical burdens for the failing heart. Perhaps the most obvious problem that occurs in the remodeled ventricle is the increase in LV end-diastolic volume, and hence end-diastolic wall stress. Insofar as the load on the ventricle at end-diastole contributes importantly to the afterload that the ventricle faces at the onset of systole, it follows that LV dilation itself will increase the work of the ventricle, and hence the oxygen use as well. In addition to the increase in LV end-diastolic volume, LV wall thinning also occurs as the ventricle begins to remodel. The increase in wall thinning along with the increase in afterload created by LV dilation leads to a functional afterload mismatch that may further contribute to a decrease in forward cardiac output. Moreover, the high end-diastolic wall stress might be expected to lead to episodic hypoperfusion of the subendocardium with resultant worsening of LV function. Finally, increased LV wall stress might lead to sustained expression of stretch-activated genes (angiotensin II, endothelin, and TNF) and/or increased oxidative stress as a result of subendocardial hypoperfusion, with the resultant activation of families of genes that are sensitive to free radical generation (eg, TNF and interleukin-1β).

A second important problem that results from increased sphericity of the ventricle is that the papillary muscles are pulled apart, resulting in incompetence of the mitral valve and the development of functional mitral regurgitation. Whereas the amount of functional mitral regurgitation was once thought to be mild, the advent of noninvasive imaging modalities has shown that functional mitral regurgitation is clinically significant. Apart from the more obvious problem of loss of forward blood flow, mitral regurgitation presents yet another problem to the heart, insofar as the mitral regurgitation results in further hemodynamic overloading of the ventricle. Taken together, the mechanical burdens engendered by LV remodeling might be expected to lead to decreased forward cardiac output, increased LV dilation (stretch), and increased hemodynamic overloading, any or all of which are sufficient to contribute to disease progression independently of the neurohormonal status of the patient. Moreover, the aforementioned changes in LV structure and function might be expected to render the cardiovascular system less responsive to normal homeostatic control mechanisms, such as increased adrenergic drive. Thus, alterations in the remodeled ventricle may foster a self-amplifying situation, in which worsening neurohormonal activation occurs in response to the inability of the remodeled LV to respond appropriately to these compensatory mechanisms. Moreover, at some point in time it is predictable that the aggregate end-organ changes that occur within the cardiomyopathic ventricle may progress to the point that no amount of neurohormonal stimulation can maintain cardiovascular homeostasis. At this point, heart failure may progress independently of the neurohormonal statues of the patient.

Are the Defects in the Geometry of the Remodeled LV Reversible?

The extant clinical experience suggests that it is possible to retard and possibly regress LV remodeling in some patients. The most obvious clinical example of reversed LV remodeling is the striking change that occurs in the dilated cardiomyopathic ventricle following implantation of a LV assist device. The salutary changes that have been reported include increased LV wall thickness, decreased LV volume, and a favorable leftward shift in the LV pressure-volume curve. Medical therapy has also been shown to halt and/or reverse LV remodeling in some patients. For example, therapy with angiotensin converting enzyme inhibitors appears to prevent worsening LV dilation and further increases in LV mass; however, it bears emphasis that these agents will not regress or reverse LV remodeling. Recently β-blockers have been shown to favorably influence LV remodeling, including improvements in LV function and a decrease in LV end-diastolic volume. Thus, the preponderance of experimental and clinical evidence suggests that the defects in the remodeled LV chamber are at least partially reversible in some patients.

LV Remodeling as a Therapeutic Target in Heart Failure

The suggestion that LV remodeling may not only be a consequence of heart failure but may also contribute to the progression of heart failure raises the interesting possibility that therapeutic strategies specifically designed to prevent and/or antagonize LV remodeling may also be beneficial in heart failure. Although it is unclear as of this writing which of the myriad of cellular and molecular mechanisms that contribute to LV remodeling should be therapeutic targets, one logical starting point would be to focus on those aspects of the remodeling process that contribute to irreversible disease progression. Thus, one attractive approach would be to develop antiremodeling strategies along 2 mutually complementary lines: preservation of cardiac myocyte cell number and maintenance of the integrity and composition of the extracellular matrix. At present, there are several intriguing possibilities with regard to preserving myocyte cell number, including strategies designed to prevent necrotic and/or apoptotic cell death, or alternatively, strategies designed to
replace lost myocytes through the use of stable myocyte implants,71 by increasing cardiac myocyte cell number through increased cell division,72 or perhaps through genetic programming of nonmyocytes (eg, fibroblasts) to myocytes. Additional approaches may also include attempts to modulate cardiac myocyte cell mass through the use of myocardial growth factors.73 Attempts to maintain the structural integrity and composition of the extracellular matrix will likely involve strategies designed to prevent excessive degradation of the extracellular matrix, as well as strategies designed to modulate excessive replacement fibrosis.74 Finally, it is important to emphasize that antiremodeling strategies need not and should not be confined to those discussed above and will likely also be extended to include a variety of novel surgical, medical, bioprosthetic, and biomechanical approaches.

Clinical Implications

In this review, we have described the clinical syndrome of heart failure in terms of 3 different clinical model systems, including cardiorenal, hemodynamic, and neurohormonal. We have also discussed the point of view that strategies designed to specifically prevent and/or attenuate LV remodeling may eventually play an important role in the clinical treatment of heart failure. However, whereas each of the established model systems explains some aspects of the syndrome of heart failure, as noted throughout this review, none of these pathophysiological models is sufficient to explain all aspects of the syndrome of heart failure. That is, each of these clinical models systems fails to encompass the whole truth about heart failure. The question that arises from the foregoing discussion is how should clinicians use these various clinical models to develop effective therapeutic strategies to treat patients with heart failure.

Given that no 1 clinical model adequately predicts and/or explains all aspects the syndrome of heart failure, it follows that clinicians should not develop therapeutic heart failure strategies based entirely on cardiorenal, hemodynamic, and neurohormonal model systems alone. Rather, clinicians should develop therapeutic strategies that combine useful elements of each of the aforementioned model systems. Moreover, the optimal choice of treatment models may vary depending on the patients clinical presentation. For example, as shown in Figure 3, the combination of cardiorenal and cardiocirculatory models is extremely useful for developing short-term strategies to treat patient symptoms related to volume overload and/or acute cardiac decompensation. Accordingly, the use of diuretics (cardiorenal model) is warranted to treat congestive symptoms, whereas the use of short-term inotropic support and/or intravenous vasodilators (cardiocirculatory model) is also clearly warranted during periods of extreme cardiac decompensation. Nonetheless, it bears emphasis that although short-term changes in cardiac output and filling pressures can favorably influence cerebral, renal, and pulmonary function, neither cardiorenal nor hemodynamic models adequately predict disease progression in heart failure. Indeed, many of the drugs that produce acute symptomatic relief in heart failure do not produce long-term benefits in heart failure and may even lead to untoward long-term clinical outcomes.7 Therefore, clinicians should not formulate intermediate or long-term treatment strategies for heart failure based entirely on cardiorenal or hemodynamic models alone. Clinicians should instead formulate long-term treatment strategies that include the use of neurohormonal antagonists known to attenuate disease progression. Accordingly, as shown in Figure 4, patients with asymptomatic and symptomatic LV dysfunction should be started and maintained on both ACE inhibitors and β-blockers in order to antagonize the renin-angiotensin and the adrenergic systems, respectively. The use of diuretic agents in combination with neurohormonal antagonists is also suggested if the patients manifest signs and symptoms related to excessive salt and water retention. Although neurohormonal antagonists may not produce acute symptomatic benefits, the overwhelming weight of clinical evidence15–17,19,75 suggests that the combined use of the appropriate pharmacological agents (Figure 4) will not only lead to improvements in quality of life, but will decrease the likelihood of disease progression and thereby decrease the risk of major cardiac events in patients with heart failure.

Heart Failure Therapy in the Coming Millennium

Despite the tremendous strides that have been achieved in the theory and therapy for heart failure over the past 2 decades, heart failure remains a relentlessly progressive disease process. Thus, our current therapy for heart failure should be viewed as an ongoing work in progress. Although the reason why heart failure progresses in patients receiving optimal therapy with ACE inhibitors and β-blockers is not known, one explanation (alluded to above) is that these agents do not directly and/or sufficiently antagonize all of the biologically active systems that become activated in the setting of heart failure. Accordingly, one logical direction for future heart failure therapies will be to develop therapeutic strategies that either more effectively antagonize the neurohormonal systems that we believe are deleterious (eg, renin angiotensin receptor blockers76), or alternatively, to develop therapeutic strategies designed to antagonize some of the other currently recognized biologically active systems that appear to play a
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