Basic Science for Clinicians

Mechanisms and Models in Heart Failure
The Biomechanical Model and Beyond

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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. 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"[1]), 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 "cardiocirculatory" or "hemodynamic" model for heart failure,[1] 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 cardiocirculatory 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. Thus, 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 cardiocirculatory 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.[1,2]

In the present review we will summarize recent advances in the field of heart failure, with a focus on the new therapeutic strategies that have been developed for treating systolic heart failure. For a complete discussion on recent advances in the diagnosis and treatment of diastolic heart failure, the interested reader is referred to several recent reviews on this topic.[3–5] To provide the proper framework for this discussion, we will review current and emerging therapies within the context of the extant conceptual biological models that clinician scientists have used for envisioning the syndrome of systolic heart failure. However, as discussed at the conclusion of this review, our current working models for heart failure are insufficient for explaining several of the new and emerging therapies for treating systolic heart failure. To this end, we suggest a simplified conceptual model for heart failure that both unites and extends several of the existing working models for heart failure.

Heart Failure as a Progressive Model

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 genetic cardiomyopathies. Regardless of the nature of the inciting event, the common feature in each of these index events is that they all, in some manner, produce a decline in pump function of the heart. In most instances patients will remain asymptomatic or minimally symptomatic after 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.

As shown in Figure 1, the compensatory mechanisms that are activated after 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. The portfolio of compensatory mechanisms that have been described include early activation of the adrenergic nervous system and salt- and water-retaining systems in order to preserve cardiac output,[6–8] as well as activation of a family of vasodilatory molecules, including natriuretic peptides, prostaglandins (PGE_2 and $PGEI_2$), and nitric oxide, to counteract the excessive vasoconstriction resulting from excessive activation of the adrenergic and renin-angiotensin systems.[9,10] However, our understanding of the family of molecules that may be involved in this process is far from complete. Although patients with depressed systolic function may remain asymptomatic or minimally symptomatic for years, at some point patients will become overtly symptomatic, with a
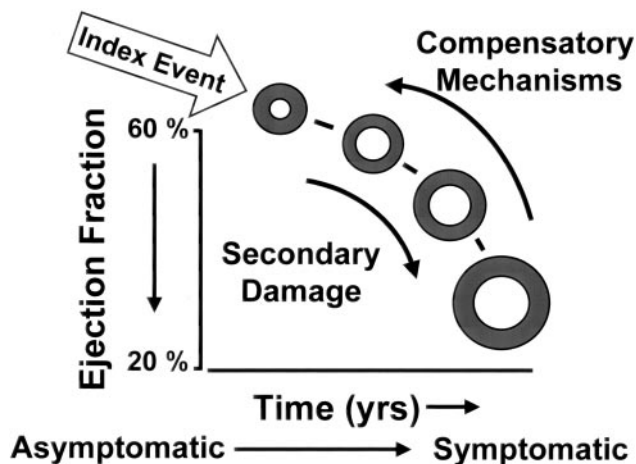
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Figure 1. Pathogenesis of heart failure. Heart failure begins after an index event produces an initial decline in pumping capacity of the heart. After this initial decline in pumping capacity of the heart, a variety of compensatory mechanisms are activated, including the adrenergic nervous system, the renin-angiotensin system, and the cytokine system. In the short term these systems are able to restore cardiovascular function to a normal homeostatic range, with the result that the patient remains asymptomatic. However, with time the sustained activation of these systems can lead to secondary end-organ damage within the ventricle, with worsening LV remodeling and subsequent cardiac decompensation. As a result of resultant worsening LV remodeling and cardiac decompensation, patients undergo the transition from asymptomatic to symptomatic heart failure.

resultant striking increase in morbidity and mortality. 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 progression occurs independently of the hemodynamic status of the patient.

Neurohormonal Mechanisms for the Progression of Heart Failure

In the latter part of the 1980s and early 1990s, evidence began to appear that certain other types of medical therapy might have a beneficial effect on the natural history of LV dysfunction or myocardial failure, despite initial hemodynamic effects that were either unimpressive[11–13] or even adverse.[11,12,14,15] These 2 types of therapies, namely, ACE inhibitors and β-adrenergic blocking agents, have dramatically changed the way in which we conceptualize heart failure. As will be discussed below, data generated from both experimental model systems and clinical trials suggest that both types of therapy may prevent the progression of pump dysfunction that characterizes the natural history of heart failure and may halt or even reverse the progressive cardiac dilatation that occurs as heart failure progresses. It is important to emphasize that the beneficial effects of these treatments are not pharmacological but rather are due to favorable effects on the biology of the failing heart. The aforementioned observations led to a point of view 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 deleterious effects on the heart and circulation.[16] "Neurohormone" is largely a 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, natriuretic peptides, and tumor necrosis factor (TNF) are peptide growth factors and/or cytokines that are produced by a variety of 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 deleterious effects that these molecules exert on the heart and circulation.

The evidence in support of the foregoing point of view is derived from 2 lines of investigation. First, a number of experimental models have shown that pathophysiologically relevant concentrations of neurohormones[17–19] or overexpression of single components of their signal transduction cascade[20–22] is sufficient to mimic some aspects of the heart failure phenotype. Second, clinical studies have shown that antagonizing neurohormones leads to clinical improvement in patients with heart failure.[23–30] Thus, a logical explanation for the progression of heart failure 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.

Thus far, a variety of proteins, including norepinephrine, angiotensin II, endothelin, aldosterone, and 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. Disease progression may also be engendered by the loss of the beneficial effects of endogenous vasodilators such as nitric oxide, natriuretic peptides, prostaglandins, and kinins, which are insufficient to counteract the peripheral vasoconstriction that results for endothelial cell dysfunction and the vasoconstrictor properties of angiotensin II and norepinephrine. The most powerful compensatory mechanism activated to support the failing heart is perhaps an increase in cardiac adrenergic drive.[31] Unlike other compensatory mechanisms, adrenergic activation accesses all the known means by which myocardial

TABLE 1.   Biological/Physiological Responses Mediated by Postjunctional Adrenergic Receptors in the Human Heart

Biological Response	Adrenergic Receptor
Beneficial effects	
Positive inotropic response	β_1, β_2 $>>\alpha_{1C}$
Positive chronotropic response	β_1, β_2
Vasodilation	β_1 (epicardial), β_2 (small vessel)
Harmful effects	
Cardiac myocyte growth	$\beta_1 > \beta_2 >> \alpha_{1C}$
Fibroblast hyperplasia	β_2
Myocyte damage/myopathy	$\beta_1 > \beta_2$, α_{1C}
Fetal gene induction	β_1
Myocyte apoptosis	β_1
Proarrhythmia	β_1, β_2, α_{1C}
Vasoconstriction	α_{1C}

performance can be stabilized or increased.[7] These include an increase in contractile function, increase in heart rate, cardiac myocyte hypertrophy, and volume expansion/increased end-diastolic volume (via β-adrenergic signaling of nonosmotic vasopressin release).[7] However, in addition to the positive effects on stabilizing myocardial performance, increased myocardial adrenergic signaling, particularly through β_1-adrenergic receptor pathways,[32] is also highly cardiomyopathic.[18,22,33] A summary of some of these helpful and harmful adrenergic receptor pathways is given in Table 1, although this table is somewhat oversimplified.

As implied by a greater number of harmful than helpful effects of activation of the adrenergic receptor pathways listed in Table 1, the net effect of a sustained increase in cardiac adrenergic activity in the failing heart is to promote myocardial disease progression and to accelerate the natural history of heart failure. Indeed, repeated observations of the salutary effects of β-blocking agents in clinical trials have shown that chronically elevated β-adrenergic signaling has adverse effects on contractile function, remodeling, and heart failure morbidity and mortality. As shown in Table 2,[134–136] these effects appear to be primarily delivered through β_1-receptor signaling, inasmuch as both β_1-receptor selective (metoprolol CR/XL and bisoprolol) or nonselective agents (carvedilol, bucindolol) have similar salutary effects in terms of molecular responses and clinical outcomes. The reasons for this are 2-fold: the increased myopathic potential of β_1-

versus β_2- or α_1-receptor signaling that is summarized in Table 1[32,34] and the binding affinity selectivity of norepinephrine for β_1 versus β_2 or α_1 receptors.[32] Thus, the beneficial effects of β-blocking agents appear to be due to the class effects of β_1-receptor blockade, at least in terms of molecular responses[35] and clinical outcomes.[28,36]

The adverse effects of β-adrenergic signaling on heart failure natural history would seem to dictate that any type of antiadrenergic therapy would be equally effective, as long as it inhibited the β_1-adrenergic signaling. However, recent clinical trial data indicate that the type of antiadrenergic therapy, particularly receptor blockade versus reducing norepinephrine release, is critically important.[37–39] The likely explanation for the polar difference in the response of these 2 general classes of antiadrenergic agents is that, during the crucial early period of adrenergic inhibition, sympatholytic agents produce an irreversible removal of adrenergic support, with inability to recruit adrenergic drive when needed to support cardiac function. In contrast, β-blockers are mass-action agents whose inhibition can be easily reversed by norepinephrine competition, which allows for retention and recruitment of the powerful adrenergic support mechanism on an as-needed basis. Extensions of these observations include the potentially favorable effects of therapeutic approaches that allow the beneficial aspects of adrenergic inotropic support to be maintained in the presence of β-blockade[40] or the addition to β-blockade to positive inotropic device therapy.[41] On the basis of experience with the β-sympatholytic agent bucindolol in the Beta-Blocker Evaluation of Survival Trial (BEST),[42] it is apparent that β-blocking agents can interact with certain characteristics of heart failure subpopulations to produce differences in clinical response. This is in contrast to the rather unvarying pharmacological properties and clinical responses to ACE inhibitors. These observations highlight the complexities encountered in therapeutic development in heart failure, wherein surprises predominate, and the only way to directly test hypotheses is in phase III clinical trials.

Of major relevance to antiadrenergic strategies in heart failure is the impact of adrenergic receptor polymorphisms on myocardial disease progression and on therapeutic response. For example, a double adrenergic receptor polymorphism, an α_{2C} deletion/loss of function genotype (α_{2C} Del322-325), combined with a high-functioning β_1-receptor genotype (β_1 Arg389), confers a 10-fold risk for the development of heart

TABLE 2.   Class Effects of β-Adrenergic Blockade in Chronic Heart Failure

Effect	Studies	β-Blockers
Reduction in total mortality	MERIT-HF,[28] CIBIS-II,[36] COPERNICUS[134]	Metoprolol CR/XL, bisoprolol, carvedilol
Reduction in CV mortality	MERIT-HF, CIBIS-II, COPERNICUS, BEST[42]	Metoprolol CR/XL, bisoprolol, carvedilol, bucindolol
Reduction in CV or HF hospitalizations	MDC,[135] CIBIS-II, MERIT-HF, COPERNICUS, US Carvedilol,[27] BEST[136]	Metoprolol tartrate, metoprolol CR/XL, bisoprolol, carvedilol, bucindolol
Improved HF symptoms	MDC, CIBIS-II, MERIT-HF, US Carvedilol	Metoprolol tartrate, metoprolol CR/XL, bisoprolol, carvedilol
Reduced need for cardiac transplantation	MDC, BEST	Metoprolol tartrate, bucindolol
Reduction in myocardial infarction	BEST[136]	Bucindolol

CV indicates cardiovascular; HF, heart failure; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; CIBIS-II, Cardiac Insufficiency Bisoprolol Study II; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Study; and MDC, Metoprolol in Dilated Cardiomyopathy Trial.

failure.[43] The α_{2C} polymorphism likely leads to a reduction in the natural brake on norepinephrine release provided by α_2 receptors, and the increased adrenergic drive in these individuals then presumably damages the heart to a greater extent in individuals with the high-functioning β_1 receptor polymorphism. Transgenic mice with genetic ablation of the α_{2C} receptor have elevated norepinephrine levels and develop evidence of cardiomyopathy.[44] Importantly, the α_{2C} polymorphism is enriched in black persons,[43] and it provides a potential explanation for certain characteristics of heart failure in this population, including worse cardiac function and prognosis per a given degree of functional incapacity. When transgenically overexpressed in mouse hearts,[45] the high-functioning β_1Arg389 receptor variant, which by prevalence is the wild-type form of the β_1-adrenergic receptor, is much more cardiomyopathic than the lower-functioning β_1Gly389 polymorphic counterpart. There is evidence from the BEST study (S. Liggett, MD, P. Lavori, MD, M.R. Bristow, MD, unpublished data, 2005) that the clinical response to bucindolol was affected in a predictable manner by these genetic variants. On the basis of these and other observations, we may be close to the time when genotyping will be a necessary prerequisite to selecting the proper treatment for chronic heart failure patients, at least in terms of antiadrenergic therapy.

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 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. Our current medical therapies for heart failure will stabilize heart failure and in some cases reverse certain aspects of the disease process. However, in the overwhelming majority of patients, heart failure will progress, albeit at a slower rate. Moreover, as heart failure progresses, many patients will be refractory and/or intolerant to conventional medical therapy and often require withdrawal of conventional medical therapies.[46] In addition, many types of neurohormonal inhibition have been shown to be ineffective or even harmful in heart failure patients (reviewed in Mann et al[47]). Although the precise mechanism(s) for this attenuation, loss, or lack of effectiveness of neurohormonal antagonism is not known, there are at least 5 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 β-blockers. A second explanation is that there may be alternative metabolic signaling for neurohormones that are not antagonized by conventional treatment strategies (eg, the conversion of angiotensin I to angiotensin II within the myocardium by tissue chymase).[48,49] Indeed, the results of recent clinical trials in which angiotensin receptor antagonists and aldosterone antagonists have been shown to have benefit when added to conventional therapy with ACE inhibitors and β-blockers clearly support this point of view.[30,50,51] Third, the

TABLE 3. Overview of LV Remodeling
Alterations in myocyte biology
Excitation contraction coupling
Myosin heavy chain (fetal) gene expression
β-Adrenergic desensitization
Hypertrophy
Myocytolysis
Cytoskeletal proteins
Myocardial changes
Myocyte loss
Necrosis
Apoptosis
Alterations in extracellular matrix
Matrix degradation
Replacement fibrosis
Alterations in LV chamber geometry
LV dilation
Increased LV sphericity
LV wall thinning
Mitral valve incompetence

currently available portfolio of neurohormonal antagonists, namely, ACE inhibitors and β-blockers, may not antagonize all of the alterations in biologically active systems that become activated in the setting of heart failure (Table 3). Indeed, given the inherent biological redundancy of all mammalian systems, it is perhaps predictable that there will be a number of 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 that are capable of contributing to disease progression. A fourth factor is that some heart failure–activated neurohormonal/cytokine signaling pathways capable of producing harmful effects in cardiac myocytes is isolated systems (eg, endothelin, TNF) may have also have favorable effects when functioning in the complex heart failure milieu. A fifth explanation for the loss of effectiveness of neurohormonal antagonism is that, at some point, 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 as a Cause of Disease Progression in 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.[52–54] Although some investigators currently view LV remodeling simply as the end-organ response that occurs after years of exposure to the deleterious effects of

TABLE 4.   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

Myocardial desynchronization

long-term neurohormonal stimulation, others have suggested that LV remodeling may contribute independently to the progression of heart failure.[52,55] Although a complete discussion of the complex changes that occur in the heart during LV remodeling is well beyond the intended scope of this brief review, it is worth emphasizing that the process of LV remodeling extends to and affects importantly the biology of the cardiac myocyte, the volume of myocyte and nonmyocyte components of the myocardium, and the geometry and architecture of the LV chamber (Table 3). Although each of these various components of the remodeling process may contribute importantly to the overall development and progression of heart failure, the reversibility of heart failure is determined by whether the changes that occur at the level of the myocyte, the myocardium, or the LV chamber are reversible. In this regard, the changes that occur at the level of the myocyte and the LV chamber appear to be at least partially reversible in some experimental and/or clinical models.[14,56–58]

A number of changes that occur during the process of LV remodeling may contribute to worsening heart failure. Principal among these changes is the increase in LV wall stress that occurs during LV remodeling. Indeed, 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 in shape.[59] As depicted in Table 4, the increase in LV size and resultant change in LV geometry from the normal prolate ellipse to a more spherical shape creates a number of de novo mechanical burdens for the failing heart, most notably an increase in LV 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 utilization 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.[60–63] Moreover, the high end-diastolic wall stress might be expected to lead to episodic hypoperfusion of the subendocardium, with resultant worsening of LV function,[64–66] as well as increased oxidative stress, with the resultant activation of families of genes that are sensitive to free radical generation (eg, TNF and interleukin-1β).

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 that are responsible for this process. 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 has an important impact on the biology of the cardiac myocyte, changes in the volume of myocyte and nonmyocyte components of the myocardium, and the geometry and architecture of the LV chamber (Table 3). Although 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

In both animal models and in the human heart, it is generally held that cardiac myocyte[67] or global pump is the primary initiating event that leads to cardiac remodeling, although remodeling can occur in the absence of myocyte dysfunction in some experimental models.[68,69] Numerous studies have suggested that failing human cardiac myocytes undergo a number of important changes that might be expected to lead to a progressive loss of contractile function, including decreased expression of α-myosin heavy chain gene with increased expression of β-myosin heavy chain,[70,71] progressive loss of myofilaments in cardiac myocytes,[72] alterations in cytoskeletal proteins,[72] alterations in excitation contraction coupling,[73] and desensitization of β-adrenergic signaling.[74] 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. Indeed, when the contractile performance of isolated failing human myocytes has been examined under very simple experimental conditions, investigators have found that there is ≈50% decrease in cell shortening in failing human cardiac myocytes compared with nonfailing human myocytes.[75] Moreover, as noted in the foregoing discussion, this defect in cell shortening has a number of important components that 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, sarcomerogenesis, 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 contractility of the failing cardiac myocyte are reversible after β-adrenergic blockade.[35,56] 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. More recent studies in patients who have been treated with β-blockers showed that patients who had an increase in their ejection fraction also had an increase in sarcoplasmic reticulum calcium ATPase mRNA and α-myosin heavy chain mRNA and a decrease in β-myosin heavy chain mRNA, thus demonstrating that the functional improvement in ventricular function after treatment with β-blockers is associated with favorable changes in myocardial gene expression. 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 relaxation compared with myocytes isolated from hearts that had not been supported with a LV assist device.[76] Although this interesting study did not directly address the mechanism for this finding, 2 recent studies may provide a partial explanation. In the first study, support with a LV assist device was shown to improve the force-frequency relationship of isolated strips of ventricular tissue, along with improvements in genes encoding for proteins involved in Ca^{2+} handling (sarcoplasmic reticulum calcium ATPase, the ryanodine receptor, and the sarcolemmal sodium-calcium exchanger).[77] In the second study, LV assist device support led to a restoration of the integrity of the dystrophin cytoskeleton, which had been shown to be disrupted in myocytes from failing hearts.[78] Together, these latter 2 studies illustrate the plasticity of the molecular phenotype in failing myocytes and suggest that alterations in calcium handling and the myocyte cytoskeleton contribute to contractile dysfunction in the failing heart.

Additional Maladaptive Changes in Remodeled, Failing Myocardial Tissue

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 the 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.[79] Indeed, concentrations of norepinephrine that are 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.[18] Moreover, excessive stimulation with either angiotensin II or endothelin has been shown to provoke myocyte necrosis in experimental models.[17] Until recently, the clinical evidence that 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 showing that levels of circulating troponin I were increased 3- to 4-fold in patients with advanced heart failure.[80] 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. Support for this point of view has increased with the recognition that DNA damage characteristic of apoptotic cell death occurs in myocytes from failing hearts.[81,82] 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 in vivo experimental model systems.[83–85] 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 intravenous inotropic support before cardiac transplantation. Given that catecholamines can provoke apoptosis in experimental models,[86] the existing clinical studies may overestimate the true frequency of apoptosis in the failing heart.[81,82] 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 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 myocyte cell loss 0.1%/y) to clinically unrealistic estimates of 5%/y to 35%/y (estimated myocyte loss >100%/y).[87] These striking disparities make it difficult to know exactly what role apoptosis plays in progressive cardiac dysfunction. Thus, although the general concept that myocyte cell loss may contribute to 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 to obtain a clearer understanding of whether cell death occurs early and continually in heart failure or whether instead cell death occurs only in end-stage hearts.

In addition to alterations in the volume and composition of the cardiac myocytes, a number of important changes occur within the extracellular matrix component of the myocardi-

um.[88–91] 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." This term has been used to describe the excessive deposition of fibrillar collagen that occurs after the death of myocytes. Enthusiasm for the point of view that progressive fibrosis plays an important role in the progression of heart failure has been engendered by experimental studies showing that angiotensin II, endothelin, and aldosterone[92–94] 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 collagen deposition has been invoked as a 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 becomes activated within the failing myocardium.[88,89,91] 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 would 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 dilation that occurs in heart failure. Although the precise biochemical triggers that are responsible for activation of MMPs are not known, it is important to note that TNF, as well as other cytokines and peptide growth factors that are expressed within the failing myocardium, is 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 the glycoproteins tissue inhibitors of matrix metalloproteinases (TIMPs), which are 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 aforementioned observations suggest that the alterations in the extracellular matrix that occur during LV remodeling are likely to be far more complex than those 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, although changes in the extracellular matrix may be partially reversible in some situations,[95–98] there is no current clinical evidence to suggest that the fibrotic changes that occur in the myocardium are completely reversible. Recent studies in which bone marrow cells or enriched hematopoietic stem cells have been delivered to adult hearts, either through intracoronary injection or direct myocardial injections[99–102] or mobilized from the periphery by administration of granulocyte colony-stimulating factor,[103] have suggested that these cells might transdifferentiate into cardiac myocytes, thereby allowing myocardial regeneration to occur. These initial findings have provoked extensive excitement in the field, which in turn has led to a number of ongoing clinical trials. Despite this initial enthusiasm, more recent studies have questioned the ability of hematopoietic stem cells to transdifferentiate into cardiac myocytes.[104–106] Indeed, Nygren and colleagues[106] have shown that the bone marrow–derived hematopoietic stem cells that engraft with cardiac myocytes are CD45 positive and α-actinin negative, suggesting that they are of hematopoietic rather than cardiac lineage. Moreover, this latter study suggested that the durability of the engrafted cells was very low after 28 days.[106] Although these and other recent studies[107,108] have raised important questions about the utility of hematopoietic stem cell transplantation in heart failure, these studies do not preclude the potential utility of nonhematopoietic-derived stem cells (eg, myocardial progenitor cells[109]) in myocardial regeneration, nor do they preclude the possibility that hematopoietic stems cells may exert beneficial effects in the heart that are distinct from their ability to regenerate the myocardium (eg, angiogenesis). Nonetheless, at the time of this writing many of the myocardial defects that occur in heart failure appear to be largely irreversible and likely represent an important contributor to disease progression in heart failure.

Alterations in Ventricular Chamber Geometry

On the basis of the foregoing discussion, it is clear that the changes that occur in the biology of the failing myocyte and 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. Several lines of evidence suggest that the deleterious changes that occur in the geometry of the remodeled left ventricle 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 also more spherical in shape.[59] As shown in Table 4, the increase in LV size and resultant change in LV geometry from the normal prolate ellipse to a more spherical shape creates a number of de novo mechanical burdens for the failing heart, as discussed above.

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."[110] Although 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 a second problem to the heart insofar as the mitral

regurgitation results in further hemodynamic overloading of the ventricle. Taken together, the mechanical burdens that are 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 make 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 left ventricle to respond appropriately to these compensatory mechanisms. Moreover, at some point 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 which point heart failure may progress independently of the neurohormonal status of the patient.

Are the Defects in the Geometry of the Remodeled Left Ventricle 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 "reverse" LV remodeling is the striking change that occurs in the dilated cardiomyopathic ventricle after implantation of a LV assist device. The salutary changes that have been reported include increased LV wall thickness,[111] decreased LV volume,[112] and a favorable leftward shift in the LV pressure-volume curve.[112] Medical therapy has also been shown to halt and/or reverse LV remodeling in some patients. For example, therapy with ACE inhibitors appears to prevent worsening LV dilation and further increases in LV mass[113,114]; however, these agents will not regress or reverse LV remodeling.[113,114] Recently, β-blockers have been shown to favorably influence LV remodeling, including improvements in LV function and a decrease in LV end-diastolic volume.[14,57,56] Moreover, recent studies employing resynchronization therapy have been shown to lead to significant decreases in mitral regurgitation and LV end-diastolic volumes.[115,116] 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 contributes 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. In addition to the beneficial effects of LV assist devices on LV remodeling, a number of different surgical approaches have been tried to prevent and/or retard LV remodeling, including surgical myoplasty, which has largely been abandoned,[117] mitral valve surgery,[118] volume reduction surgery (partial left ventriculectomy [so-called Batista procedure]),[119] endoventricular circular patch plasty/surgical ante-
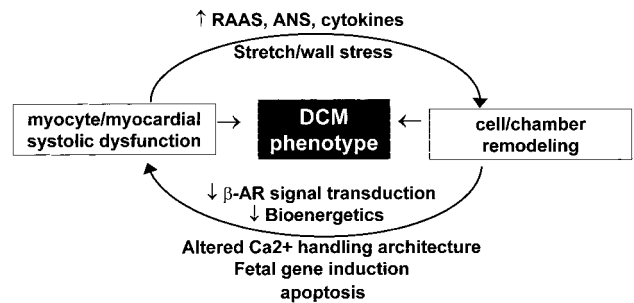

Figure 2. Interrelationship between contractile dysfunction and cardiac remodeling. The close relationship between the development of contractile dysfunction and cardiac remodeling is responsible for disease progression in primary or secondary dilated cardiomyopathy (DCM). RAAS indicates renin-angiotensin-aldosterone system; ANS, adrenergic nervous system; and AR, adrenergic receptor. Reproduced with permission from *Heart Disease: A Textbook of Cardiovascular Medicine*. Philadelphia, Pa: WB Saunders; 2004.[133]

rior ventricular restoration (so-called Dor procedure),[120] and cardiac assist support devices.[58,121,122]

Summary, Clinical Implications, and Future Developments

In the present review we have described the clinical syndrome of heart failure in terms of several different clinical model systems, including a cardiorenal model, a hemodynamic model, and a neurohormonal model. As noted, each of the models has strengths and weaknesses in terms of understanding the mechanisms responsible for heart failure and developing effective new therapies for heart failure. We also discussed the importance of the interaction between myocardial systolic dysfunction and cardiac remodeling in the development and progression of heart failure. As illustrated in Figure 2, these 2 fundamental components of the heart failure phenotype are closely interrelated, such that the development of one of them in isolation will usually contribute to the development of the other. Viewed together, these observations suggest that heart failure can be viewed as a biomechanical model, in which heart failure develops and progresses as a result of the deleterious changes in cardiac function and cardiac remodeling that occur as the result of sustained neurohormonal activation. Although this point of view does not obviate the importance of neurohormonal activation in the setting of heart failure, it extends the insights provided by this paradigm by focusing the treatment of heart failure on the downstream biological consequences of neurohormonal activation rather than on neurohormonal activation per se. Thus, clinicians should not only tailor therapeutic strategies to treat their patients' symptoms (eg, diuretics and digitalis) but should also provide therapies that affect the adverse biological consequences of sustained neurohormonal activation (eg, ACE inhibitors, β-blockers, and aldosterone antagonists). One important departure of the biomechanical model from the neurohormonal model is that the biomechanical predicts that at some point heart failure will progress independently of the neurohormonal status of the patients. Thus, when the deleterious changes in cardiac function and cardiac remodeling are sufficiently advanced, they become
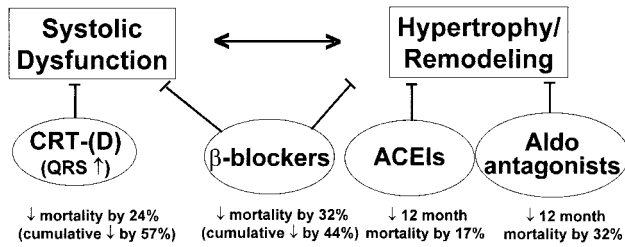
Figure 3. Effect of medical therapies that affect the natural history of heart failure based on the primary site of action. CRT-(D) indicates cardiac resynchronization therapy plus defibrillator; ACEIs, angiotensin-converting enzyme inhibitors; and Aldo, aldosterone.

self-sustaining and hence are capable of driving disease progression independently of the neurohormonal status of the patient. This may help to explain, at least in part, why conventional neurohormonal strategies lose effectiveness in end-stage heart failure,[46] as well as why many device-based therapies that concurrently affect LV pump performance and LV remodeling (eg, cardiac resynchronization) are beneficial.

The biomechanical model predicts that therapeutic strategies that are designed to interrupt the viscous cycle of myocardial dysfunction and/or cardiac remodeling will favorably affect the heart failure phenotype and the natural history of heart failure progression. In designing such therapies, it makes sense to target molecular mechanisms that are operative within the pathological contexts of myocardial dysfunction and/or cardiac remodeling, such that their correction involves normalization of mechanisms that have become maladaptively upregulated or downregulated in direct relation to the development of the heart failure phenotype. Moreover, it makes sense to target molecular mechanisms that will affect both cardiac function and cardiac remodeling rather than treating either of these 2 components in isolation. In this context, it is useful to review how existing therapeutic interventions in heart failure affect myocardial systolic function and cardiac remodeling. As illustrated in Figure 3, ACE inhibitors prevent cardiac remodeling but have very modest overall effects on cardiac performance.[123] On the other hand, β-adrenergic blocking agents lead to improvements in pump performance as well as reverse cardiac remodeling, as discussed in detail above. Moreover, considerable additional potential exists for improved targeting of the renin-angiotensin system, as demonstrated by the Randomized Aldactone Evaluation Study (RALES),[29] Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS),[51] and Candesartan in Heart Failure Morbidity and Mortality Assessment–Added[124] (CHARM-Added) trials. The development of cardiac resynchronization therapy, a treatment that instantaneously improves systolic pump function[40,125,126] by eliminating chamber contractile dyssynchrony caused by delayed intraventricular conduction, ultimately reverses remodeling[116,127] and improves the natural history of heart failure (reviewed by Abraham and Hayes[128]). Indeed, in the recently reported Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial, the reduction in mortality by cardiac resynchronization therapy alone was statistically marginal ($P=0.059$) but nu-

merically substantial (by 24%) and was due entirely to a reduction in pump function deaths.[40]

Where Will Future Advances in the Field of Heart Failure Lead Over the Next 5 to 10 Years?

In the context of the foregoing discussion, it will be interesting to see whether new therapies that affect both myocardial function and cardiac remodeling will improve the natural history of heart failure. For example, therapies that directly affect cardiac remodeling, such as passive cardiac support devices,[58,129] surgical restoration of LV shape (eg, the Dor procedure),[130] and stem cells are currently undergoing clinical trials and may find their way into routine clinical use within the next 5 years. Alternatively, newer agents that increase inotropic support of the heart without unwanted proarrhythmic effects, including low-dose type III phosphodiesterase inhibitors combined with β-blockers (eg, enoximone),[41] type III phosphodiesterase inhibitors that sensitize the myofilaments to Ca^{2+} (eg, levosimendan),[131] or phospholamban inhibitors[132] are undergoing evaluation and, if proven to be safe, may be used earlier in the disease process to prevent and/or retard the development of cardiac deterioration. Additional benefits may also be derived from more optimal inhibition of the adrenergic nervous system, such as by targeting hyperresponder genetic variants in adrenergic receptors, as well as by more optimal correction of dyssynchronous ventricular chamber contraction by targeting ventricles with directly demonstrated dyssynchrony regardless of QRS length. In addition, it is obvious from even a superficial inspection of the elements of Figure 2 that there are multiple opportunities for developing new successful heart failure therapies. These would include pharmacological inhibitors that block final common signal transduction pathways that have been linked to pathological hypertrophy, which would be used to prevent LV remodeling and hence retard disease progression. Such drugs include agents that inhibit calcineurin signaling or protein kinase C signaling or drugs that inhibit the transcriptional activation of fetal contractile protein genes (eg, MEF2 inhibitors, class I histone deacetylase inhibitors). Many of these approaches are actually undergoing systematic development, and it is likely that at least some of them will be successful.

Acknowledgments

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