Clin. Cardiol. Vol. 21 (Suppl I), I-14–I-19 (1998)

Cardiac Remodeling as a Consequence and Cause of Progressive Heart Failure

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Summary: Natural history studies in heart failure have shown that increases in left ventricular (LV) volume and LV mass are directly related to future deterioration in LV performance and a less favorable clinical course. Despite the recognized importance of remodeling in heart failure, very little is known about the basic mechanisms that lead to cardiac remodeling. In this review, we will summarize recent clinical and experimental studies that highlight the importance of the remodeling process during the progression of heart failure. The intent of this review is to provide an integrated view of the mechanisms that contribute to LV remodeling at the cellular level, the myocardial level, and the level of the chamber.

Key words: left ventricular remodeling, heart failure, cardiac myocyte, apoptosis, necrosis

Introduction

Conceptually, heart failure may be viewed as a progressive disorder that is initiated after an "index event" damages the heart muscle, with a resultant decline in the number of functioning cardiac myocytes and a concomitant decline in the pumping capacity of the heart. As shown in Figure 1, the exact nature of the index event may vary. For example, heart failure may supervene following acute myocardial ischemia and/or infarction, sustained hemodynamic pressure or volume overloading, or myocardial inflammation secondary to myocarditis. It is also recognized that a variety of hereditary disorders, most notably those affecting the cytoskeleton, may also produce an initial decline in the pumping capacity of the heart.[1] Clinical studies suggest that, in general, most patients will remain asymptomatic following the initial decline in pumping capacity of the heart. However, at some point (which may range from days to years), the vast majority of patients will make the transition from asymptomatic to symptomatic heart failure. Figure 1 shows that as patients transition to symptomatic heart failure, their hearts undergo a process known as "left ventricular (LV) remodeling," wherein there is not only an increase in the overall size of the heart, but there are also alterations in the shape of the heart, such that it assumes a more spherical geometry. The changes in chamber shape and size are also accompanied by a further decline in the overall pumping capacity of the heart. Whereas LV remodeling was once viewed as a consequence of the activation of a number of compensatory mechanisms that were sufficient to produce direct toxic effects on the heart and circulation, there is increasing evidence that the process of LV remodeling may itself contribute to progression of disease in heart failure. Indeed, natural history studies have shown repeatedly that increases in LV volume and mass have been closely linked to future deterioration in LV performance and a less favorable clinical course.[2–4] Given the central importance of LV remodeling as a potential cause and consequence of heart failure, this review will focus on the basic cellular and molecular mechanisms that are responsible for this process.

This work was supported, in part, by research funds from the Department of Veterans Affairs and the N.I.H. (RO1 HL58081-01A1 and P50 HL-O6H).

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Left Ventricular Remodeling

For the purpose of this review, we will define LV remodeling as a change in LV chamber and volume that is not related to preload-mediated increase in sarcomere length.[2,5] Although the complex changes that occur in the heart during LV remodeling have commonly been described in mechanical and/or anatomic terms, as shown in Table I, LV remodeling involves important alterations in the biology of the cardiac myocyte, changes in volume of myocyte and nonmyocyte components

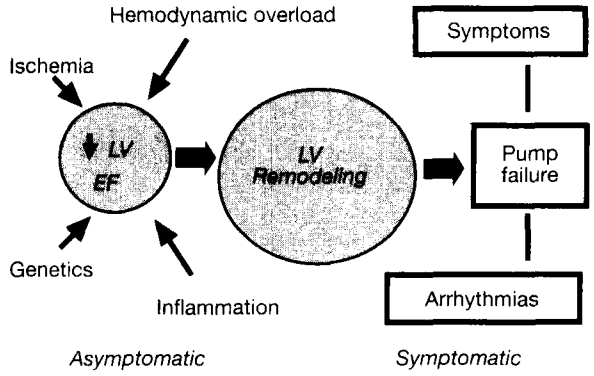

FIG. 1 Pathogenesis of heart failure. Heart failure begins after one or more different forms of environmental stress damage to the myocardium, with a resultant decline in pumping capacity of the heart. Following this initial decline, patients remain asymptomatic. However, as patients develop symptoms, their hearts undergo left ventricular (LV) remodeling, wherein there is an increase in LV size and a further decline in LV pumping capacity.

TABLE I Overview of left ventricular remodeling

Alterations in myocyte biology
Excitation contraction coupling
Myosin heavy chain (fetal) gene expression
β-adrenergic desensitization
Hypertrophy with loss of myofilaments
Cytoskeletal proteins
Myocardial changes
Myocyte loss
Necrosis
Apoptosis
Alterations in extracellular matrix
Matrix degradation
Replacement fibrosis
Alterations in left ventricular chamber geometry
Increased wall stress
Mitral valve incompetence
Wall thinning with afterload mismatch

of the myocardium, as well as alterations in the chamber geometry and architecture of the heart. Although each of these components may contribute importantly to the overall development and progression of heart failure, it is becoming increasingly unlikely that any single defect or any single aspect of the remodeling process itself will satisfactorily explain the progressive cardiac decompensation that occurs as heart failure advances. Accordingly, the discussion that follows will attempt to discuss the changes that occur in the cell, the tissue, and the chamber in an integrative manner.

Alterations in the Biology of the Cardiac Myocyte

Numerous studies have suggested that several important alterations occur at the level of the failing human cardiac myocyte, including decreased α-myosin heavy chain gene expression with a concomitant increase in β-myosin heavy chain expression,[6] progressive loss of myofilaments in cardiac myocytes,[7] alterations in cytoskeletal proteins,[7] alterations in excitation contraction coupling,[8] as well as desensitization of beta-adrenergic signaling.[9] Taken together, these changes would be expected to lead to a defect in myocyte contractile function and 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 an approximately 50% decrease in cell shortening in failing human cardiac myocytes when compared with nonfailing human myocytes.[10] Moreover, as noted in the foregoing discussion, this defect in cell shortening has a number of important components that act in combination to produce the observed phenotype of cellular contractile dysfunction. An important corollary of this statement is that simplistic and/or reductionist attempts to isolate and define the defect in myocyte dysfunction as single "hit" or a single gene problem will likely be unrewarding, insofar as each of the defects described here is sufficient to produce some form of contractile dysfunction. Thus, the contractile dysfunction that develops within myocytes during the process of LV remodeling is likely to involve families of genes including those that regulate calcium handling, sarcomerogenesis, beta-adrenergic signaling, and the cytoskeleton, all of which may interact in an exceedingly complex manner within the cardiac myocyte. Thus, strategies that are designed to elucidate the cause(s) of the alterations in the biology of the myocyte are likely to have more therapeutic import than strategies that are designed to treat the consequences of altered contractile dysfunction of the failing cardiac myocyte.[11,12]

Are the Defects in Cell Shortening in Cardiac Myocytes Reversible?

From a therapeutic standpoint, one would like to know whether the alterations in the biology of the failing myocyte are reversible. Although it is unclear from clinical studies whether the changes that occur at the level of the myocyte are reversible, the existing experimental literature suggests that alterations in the biology of the failing myocyte are reversible following beta-adrenergic blockade.[13] The mechanism for the improved contractile performance in isolated myocytes was not determined precisely but was associated with an increase in the density of myofilaments within the myocytes themselves. Thus, in this experimental model, beta-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 patients with heart failure patients placed on beta-adrenergic blocking agents[14] is the result of the reversal of unfavorable alterations in the biology of the adult myocyte remains speculative for the present. Recently, it has been noted that isolated failing

myocytes obtained from hearts that had been supported with an LV assist had improved shortening and responsiveness to isoproterenol compared with myocytes isolated from hearts that had not been supported with an LV assist device.[15] Although, this 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 changes that occur in failing myocardium may be discussed in terms of changes that occur in cardiac myocytes as well as changes that occur in the extracellular matrix. With respect to the changes occurring in cardiac myocyte component of the myocardium, there is now increasing evidence that myocyte loss through both necrotic and apoptotic cell death may lead or contribute to progressive cardiac dysfunction and LV remodeling. For example, it has long been postulated that excessive adrenergic drive might be overtly toxic to the myocardium[16] by triggering necrotic cell death; moreover, 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 (Fig. 2).[17] Furthermore, myocyte necrosis may also be provoked as a result of excessive stimulation with either angiotensin II or endothelin in experimental models.[18] However, in comparison with the simplicity of these experimental studies in which cause and effect are relatively easy to discern, it has been comparatively harder to demonstrate the toxic effects of norepinephrine (or any other neurohormone) because of the inherent difficulties in demonstrating the presence of contraction band necrosis (the hallmark of myocyte necrosis) in histologic specimens of failing myocardium. Recently, however, Missov *et al.* have shown that levels of circulating troponin I are increased three- to fourfold in patients with advanced heart failure, suggesting that there is ongoing myocyte necrosis in patients with heart failure.[19]

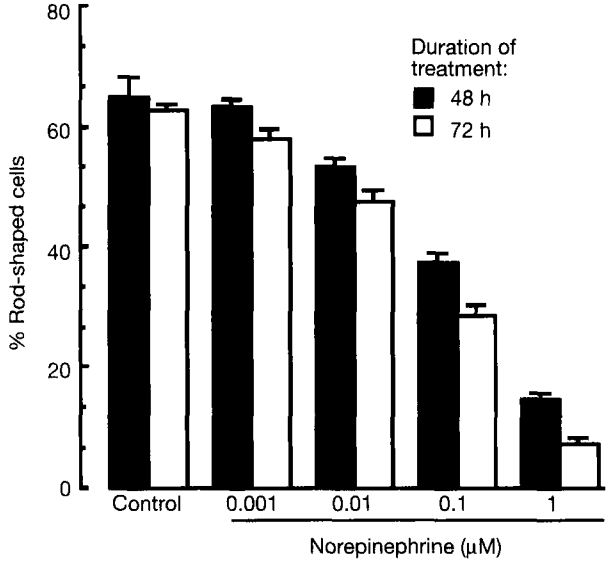

FIG. 2 Effect of norepinephrine on cardiac myocyte viability. Concentrations of norepinephrine that are available within failing myocardium are sufficient to produce cytotoxicity in isolated cardiac myocytes. For each concentration of norepinephrine shown, the data represent the mean ± standard error values from a minimum of 16 dishes obtained from a minimum of four primary cardiac myocyte isolations. Cardiac myocyte viability, expressed in terms of the percentage of rod-shaped cells in culture, was adversely affected by increasing concentrations of norepinephrine. Analysis of variance indicated that this catecholamine-mediated toxic effect was both concentration-dependent and time-dependent. Reproduced from Ref. No. 17 with permission.

The relatively recent recognition that mammalian cells are capable of undergoing apoptosis, or programmed cell, death has prompted the intriguing thought that apoptosis might also contribute to progression of disease by provoking cell death and hence myocardial dysfunction. This point of view has received increasing support with the recognition that myocytes in failing myocardium have DNA damage that is characteristic of apoptotic cell death.[20,21] Moreover, many of the factors that have been implicated in the pathogenesis of heart failure—including myocardial stretch, norepinephrine, tumor necrosis factor-α (TNF-α), oxidative stress and angiotensin II—have been shown to produce apoptosis in a variety of simple in vitro and in vivo experimental model systems.[22–24] Nonetheless, despite the undeniable appeal of programmed cell death as an important mechanism for progression of disease in the failing heart, there are at least three caveats that warrant discussion. First, the only assessments with respect to the frequency of myocyte apoptosis in failing myocardial tissue have been performed in explanted hearts obtained from patients on a cardiac transplantation list, many of whom were receiving intravenous inotropic support prior to cardiac transplantation. Given that catecholamines can provoke apoptosis in experimental models, the existing studies may overestimate the true frequency of apoptosis in the failing heart.[20,21] Second, there are no data with respect to whether myocyte apoptosis occurs in patients with mild to moderate heart failure. Thus, it is not clear to what extent apoptosis actually contributes to progression of disease in heart failure. Third, the current estimates of myocyte apoptosis in failing myocardium range from clinically significant levels of approximately 0.25%/year (estimated myocyte cell loss approximately 3 to 4%/ year) to clinically impossible estimates of approximately 5 to 35%/year (estimated myocyte loss > 100%/year). These striking disparities make it difficult to know exactly what contribution apoptosis plays in progressive cardiac dysfunction. Finally, it should be emphasized that quantitative determinations of total myocyte cell number in explanted hearts from patients with dilated cardiomyopathies do not suggest a significant loss of cardiac myocytes.[25] Thus, although the general concept that myocyte cell loss contributes to progressive myocardial dysfunction is appealing and is likely to have some validity, further clinical studies will be necessary to determine exactly to what extent myocyte cell loss through necrosis and apoptosis contribute to progressive myocardial dysfunction.

Although alterations in the volume and composition of the cardiac myocytes have traditionally been the focus of studies on LV remodeling, there is increasing evidence that a number of important alterations occur within the extracellular matrix component of the myocardium as well. The most widely recognized defects that occur in the extracellular matrix are 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 around myocytes. In the setting of heart failure, it is presumed that the excessive deposition of fibrous tissue occurs following the death of myocytes. Experimental heart failure models, wherein catecholamines have been used to provoke myocyte necrosis, support this point of view and show that excessive fibrillar collagen is deposited in the areas of myocyte loss.[26] Further enthusiasm for the point of view that fibrosis plays an important role in the progression of heart failure originates from experimental studies that have shown that a variety of circulating "neurohormones" that are elevated in patients with heart failure, including angiotensin II and endothelin,[27–29] are sufficient to trigger excessive fibrosis in myocardial tissue, thus providing a potential biochemical explanation for the development of excessive fibrosis in heart failure. Although excessive deposition of fibrin might be expected to contribute to progressive myocardial dysfunction by preventing myocyte shortening, the changes in fibrillar collagen of the failing myocardium are important for a second reason: that is, the fibrillar collagen weave that surrounds and interconnects the myocytes is responsible for efficient force generation in the myocardium.[26,30] For example Mo^{v} mice that are deficient in the ability to crosslink collagen will develop contractile dysfunction.[26] Germane to this discussion is the observation that, in failing myocardial tissue, there is progressive loss of fibrillar type 1 collagen that invests and interconnects the myocytes and a progressive increase of type 3 collagen between the myocytes.[31] These alterations in the arrangement and type of fibrillar collagen might also be expected to lead to ineffective generation of force in myocardial tissue.

Although excessive fibrin deposition has been invoked as one logical explanation for the progressive contractile dysfunction that occurs in the failing heart, it has been diffi-cult until recently 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 family collagenolytic enzymes are activated within the failing myocardium.[32,33] 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 the dilation that occurs in heart failure. Although the precise biochemical triggers that are responsible for activation of MMPs are not known, a recent experimental study has shown that pathophysiologically relevant concentrations of TNF-α are sufficient to produce LV remodeling and degradation of the fibrillar collagen weave around the cardiac myocytes.[34] Given that TNF-α, and other cytokines and peptide growth factors that are expressed within the failing myocardium are capable of activating MMPs, it is likely that a number of factors may contribute to progressive MMP activation within the failing heart. Although progressive activation of MMPs provides a satisfying explanation for the LV dilation and remodeling that occurs as heart failure advances, the biology of matrix remodeling in heart failure is likely to be much more complex. Given the central importance of the extracellular matrix in maintaining tissue integrity, it is not surprising that nature has developed a number of methods for regulating the activation and expression of MMPs. Relevant to this discussion is the recent finding that several glycoproteins termed *tissue inhibitors of matrix metalloproteinases (TIMPs)* are capable of regulating the activation of MMPs by forming a 1:1 stochiometric complex with both latent and activated MMP complexes, thus preventing these enzymes from degrading the collagen matrix of the heart. Viewed together, these observations suggest that the critical balance between fibrillar collagen deposition and fibrillar collagen degradation is controlled, at least in part, by the stoichiometric balance between activators of the collagenolytic cascade (e.g., MMPs and inhibitors of the collagenolytic cascade) such as the TIMPs (Fig. 3). However, the exact role of TIMPs in the failing heart is far from clear; 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, these observations suggest that the alterations that occur in the extracellular matrix during LV remodeling are likely to be far more complex than was previously supposed and that there may be periods of ongoing fibrin degradation and deposition throughout the process of LV remodeling.

Alterations in Ventricular Chamber Geometry

One of the earliest observations with respect to LV remodeling was the finding that the remodeling heart assumed not

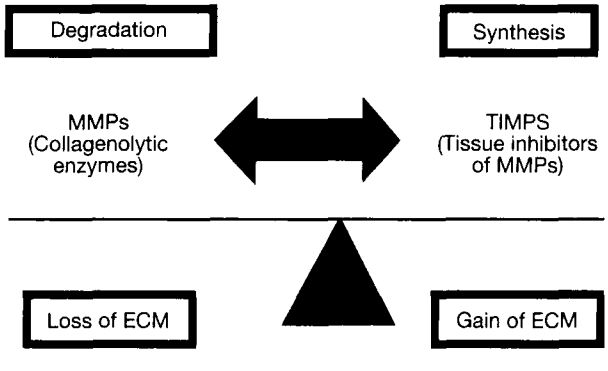

FIG. 3 Remodeling of the extracellular matrix (ECM). The volume and composition of the extracelluar matrix exists as a balance between enzymatic proteins that degrade the extracellular matrix [matrix metalloproteinases (MMPs)] and glycoproteins that inhibit this degradation [tissue inhibitors of matrix metalloproteinases (TIMPs)].

only a larger shape, but also a more spherical shape. The resultant change in LV geometry from the normal prolate ellipse to a more spherical shape places the ventricle at a mechanical disadvantage. As reviewed in Table II, the increase in chamber size creates a number of "new" mechanical burdens for the failing heart that are independent of those that occur at the cellular and tissue levels but that can act in a combinatorial manner with the aforementioned defects that occur at the cellular and tissue levels. Perhaps the most obvious problem that occurs in the remodeling ventricle is the increase in LV end-diastolic dimension and, hence, end-diastolic wall stress. Because 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 use of oxygen as well. In addition, as noted here, LV wall thinning 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 can also lead to a decrease in forward cardiac output.[35] Moreover, the high end-diastolic wall stress might be expected to lead to episodic hypoperfusion of the subendocardium, with resultant episodic worsening of LV function. A second important problem that occurs with 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."[36] Although the amount of functional mitral regurgitation was once thought to be mild, the advent of noninvasive imaging modalities, most notably Doppler echocardiography, has shown that functional mitral regurgitation is more significant than previously supposed. Apart from the more obvious problem of loss of forward blood flow, mitral regurgitation presents a second problem to the heart insofar as the mitral regurgitation results in further hemodynamic overloading of the ventricle. Taken together, the mechanical problems that are engendered by LV remodeling might be expected to lead to decreased forward cardiac output and increased LV dilation (stretch), both of which are sufficient to lead to worsening activation of compensatory neurohormonal mechanisms.

Are the Defects in Left Ventricular Geometry in the Remodeled Ventricle Reversible?

Although a number of surgical approaches have been tried to prevent and/or retard LV remodeling, including surgical myoplasty and volume reduction surgery,[37] none of these approaches has received widespread acceptance. With regard to medical therapy, it has been shown that angiotensin-converting enzyme (ACE) inhibitors will prevent worsening LV dilation and increase in LV mass; however, these agents will not regress or reverse LV remodeling.[38,39] Recently, it has been shown that beta blockers will favorably influence LV remodeling and lead not only to improvements in LV function, but a decrease in LV volumes as well.[14,40] Thus, it is tempting to speculate that one of the mechanisms for the salutary effects of beta-blocking agents is their effect on LV remodeling.

TABLE II Mechanical disadvantages created by left ventricular remodeling

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

Conclusion

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 or clinical terms is that the clinical syndrome of heart failure almost certainly represents the summation of multiple anatomic, functional, and biologic alterations that interact together in an exceedingly complex manner and in different genetic and environmental backgrounds over a sustained (but variable) period of time. In the foregoing review, we have attempted to discuss the mechanisms that contribute to the process of LV remodeling in the failing heart. The consistent theme that we have tried to develop throughout this discussion is that remodeling is an exceedingly complex process that occurs simultaneously at the cellular and molecular level, the myocardial level, and the level of the ventricular chamber as whole. Thus, remodeling may be viewed both as an adaptive *consequence* of the initial damage to the myocardium as well as the ensuing damage that occurs following the excessive activation of compensatory mechanisms, and as a *cause* of progressive heart failure, insofar as the changes that occur within the remodeled ventricle can lead to worsening pump function and arrhythmias. Accordingly, attempts to interdict specific aspects of remodeling without considering the biology of remodeling as a whole may be less rewarding than attempts to delineate the basic mechanisms that are responsible for the process of LV remodeling.

Acknowledgments

The authors acknowledge the secretarial assistance of Jana Grana and would also like to thank Dr. Andrew I. Schafer for his past and present support.

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