

STATE-OF-THE-ART PAPER

Myocardial Recovery and the Failing Heart

Myth, Magic, or Molecular Target?

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Medical and device therapies that reduce heart failure morbidity and mortality also lead to decreased left ventricular volume and mass and a more normal elliptical shape of the ventricle. These are due to changes in myocyte size, structure, and organization that have been referred to collectively as reverse remodeling. Moreover, there are subsets of patients whose hearts have undergone reverse remodeling either spontaneously or after medical or device therapies and whose clinical course is associated with freedom from future heart failure events. This phenomenon has been referred to as myocardial recovery. Despite the frequent interchangeable use of the terms “myocardial recovery” and “reverse remodeling” to describe the reversal of various aspects of the heart failure phenotype after medical and device therapy, the literature suggests that there are important differences between these 2 phenomena and that myocardial recovery and reverse remodeling are not synonymous. In this review, we discuss the biology of cardiac remodeling, cardiac reverse remodeling, and myocardial recovery with the intent to provide a conceptual framework for understanding myocardial recovery. (J Am Coll Cardiol 2012;60:2465–72) © 2012 by the American College of Cardiology Foundation

Clinical studies have shown that medical and device therapies that reduce heart failure morbidity and mortality also lead to decreased left ventricular (LV) volume and mass and restore a more normal elliptical shape to the ventricle. These salutary changes represent the summation of a series of integrated biological changes in cardiac myocyte size and function, as well as modifications in LV structure and organization that are accompanied by shifts of the LV end-diastolic pressure–volume relationship (EDPVR) toward normal. For want of better terminology, these changes have been referred to collectively as reverse remodeling (1,2). It has also become clear that there are subsets of patients whose hearts have undergone reverse remodeling either spontaneously or after medical or device therapies and whose clinical course is associated with freedom from future heart failure events. This latter phenomenon is referred to as myocardial recovery (3). The exciting observations with respect to reverse remodeling and myocardial recovery have engendered a great deal of interest, insofar as they may provide important new insights into the development of novel therapies that are designed to reverse and/or possibly cure heart failure as opposed to the current therapeutic

approaches that focus on preventing disease progression by blocking the body’s homeostatic responses (e.g., neurohormonal activation). Despite the frequent interchangeable use of the terms “myocardial recovery” and “reverse remodeling” to describe the reversal of various aspects of the heart failure phenotype after medical and device therapy, the extant literature suggests that there are important differences between these 2 phenomena and that myocardial recovery and reverse remodeling are not synonymous. Although there is abundant phenomenological annotation of the components of reverse remodeling, it is unclear at the time of this writing what components of the process of reverse remodeling are necessary to achieve myocardial recovery. In this review, we discuss the biology of cardiac remodeling, cardiac reverse remodeling, and myocardial recovery, with the intent to provide a conceptual framework for understanding myocardial recovery.

Cardiac Remodeling

The term “LV remodeling” describes the changes in LV mass, volume, shape, and composition of the ventricle in response to the mechanical (stress and strain) and systemic neurohormonal activation. Remodeling can be physiological (as in normal growth of an organism, mild sustained hypertension, or exercise training) or pathological (as in the case of systolic heart failure). In either case, changes in the volume and biology of the cardiac myocytes and/or changes in the quantity and composition of the extracellular matrix (ECM) underlie remodeling of the ventricular chamber (Table 1). Remodeling can be observed in any of the 4 cardiac

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**Abbreviations
and Acronyms**

- ECM** = extracellular matrix
- EDPVR** = end-diastolic pressure-volume relationship
- LV** = left ventricular
- LVAD** = left ventricular assist device

chambers. Although a number of reviews have summarized the changes that occur at the cellular, molecular, and anatomic level during cardiac remodeling (4), far fewer studies have focused on the factors that allow the heart to revert to normal LV size and shape (i.e., reverse remodeling). Insofar as the primary purpose of this review is to focus on myo-

cardial recovery, we only discuss the biology of cardiac remodeling briefly to provide the requisite background for the subsequent discussion of the biology of reverse remodeling and myocardial recovery (see reference [5] for citations).

The changes that occur in the biology of the failing adult cardiac myocyte include: 1) cell hypertrophy; 2) changes in excitation-contraction coupling leading to alterations in the contractile properties of the myocyte; 3) progressive loss of myofilaments (myocytolysis); 4) β -adrenergic desensitization; 5) abnormal myocardial energetics secondary to mitochondrial abnormalities and altered substrate metabolism; and 6) progressive loss and/or disarray of the cytoskeleton. Collectively these changes lead to decreased shortening and delayed relaxation of the failing cardiac myocyte. The alterations that occur in failing myocardium may be categorized into those that occur in the volume of cardiac myocytes as well as changes that occur in the volume and composition of the ECM. 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, via necrotic, apoptotic, or autophagic cell death pathways, may contribute to progressive cardiac dysfunction and LV remodeling. What is less well understood is the critical mass of functioning myocytes that is necessary to maintain preserved LV pump function, as well as the contribution of stem cells (endogenous or bone marrow derived) to maintaining this critical mass.

Changes within the ECM constitute the second important myocardial adaptation that occurs during cardiac remodeling and include changes in overall collagen content, the relative contents of different collagen subtypes, collagen cross-linking, and connections between cells and the ECM via integrins. Furthermore, the 3-dimensional organization of the ECM provides the physical scaffold that allows cardiac myocytes to remain properly oriented and aligned for the efficient transduction of myocyte shortening into developed ventricular pressure. All of these essential features of the ECM become altered and distorted in heart failure secondary to alterations in collagen metabolism, which, in turn, are due to changes in the balance between matrix metalloproteinase inhibitors and activators and changes in collagen subtype expression. The changes that occur in the biology of the cardiac myocyte as well as the myocardium (cardiocytes and ECM) lead to progressive LV dilation and

increased sphericity of the ventricle. The resultant increase in LV end-diastolic volume along with concomitant LV wall thinning that can occur in some settings, set the stage for progressive functional ventricular afterload mismatch that contributes further to a decrease in stroke volume. Moreover, the high end-diastolic wall stress might be expected to lead to: 1) hypoperfusion of the subendocardium, with resultant ischemia and worsening of LV function; 2) increased oxidative stress with resultant activation of families of genes that are sensitive to free radical generation (e.g., tumor necrosis factor and interleukin-1 β); and 3) sustained expression of stretch-activated genes (angiotensin II, endothelin, and tumor necrosis factor) and/or stretch activation of hypertrophic signaling pathways. Increasing LV dilation also results in tethering of the papillary muscles with resultant incompetence of the mitral valve apparatus and functional mitral regurgitation and further hemodynamic overloading of the ventricle. Taken together, the mechanical burdens that are engendered by LV remodeling contribute to disease progression independent of the neurohormonal status of the patient.

Reverse Remodeling

The term “reverse remodeling” was first used to describe the leftward shift in the LV end-diastolic pressure-volume curve of the failing heart after hemodynamic unloading with a left ventricular assist device (LVAD) or a myocardial wrap with the latissimus dorsi muscle (1,2). An important feature of the decrease in LV size with reverse remodeling is that the change in LV geometry persisted even if the inciting therapy was abruptly stopped, suggesting that the change in properties reflected intrinsic biological changes in the LV chamber as opposed to changes in LV volume that occur simply

Table 1 Overview of Cardiac Remodeling

Myocyte defects
Hypertrophy
Fetal gene expression
Beta-adrenergic desensitization
Myocytolysis
Excitation contraction coupling
Cytoskeletal proteins
Myocyte energetics
Myocardial defects
Myocyte death
Apoptosis
Necrosis
Autophagy
Alterations in extracellular matrix
Matrix degradation
Replacement fibrosis
Angiogenesis
Abnormal left ventricular geometry
Left ventricular dilation
Left ventricular wall thinning
Mitral valve incompetence

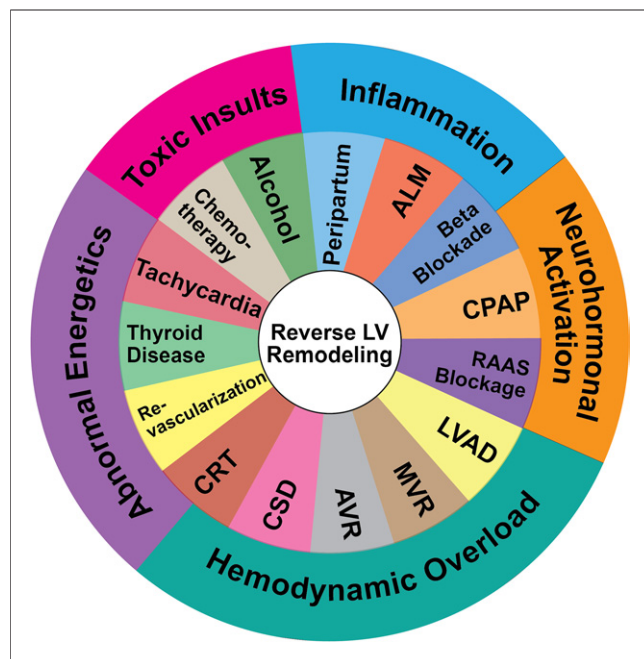


Figure 1 Reverse Remodeling in Clinical Settings

Reverse remodeling is observed in a variety of clinical settings, as shown in the middle ring of the diagram. The segments illustrated in the outermost ring highlight the pathophysiological processes implicated by reverse remodeling in each particular clinical setting. ALM = acute lymphocytic myocarditis; AVR = aortic valve replacement; CPAP = continuous positive airway pressure; CRT = cardiac resynchronization therapy; CSD = cardiac support device; LVAD = left ventricular assist device; MVR = mitral valve repair/replacement; RAAS = renin-angiotensin-aldosterone system. Modified from Hellawell and Margulies (6).

in response to a decrease in LV filling pressure. As shown in Figure 1, reverse remodeling has been observed in a wide variety of clinical settings, even when the severity of heart failure is quite severe, including viral myocarditis and postpartum cardiomyopathy or after removal of a cytotoxic agent. There is also extensive clinical trial-based evidence supporting the potential for reverse remodeling in patients with chronic heart failure who have received medical, device-based, and surgical interventions (reviewed in references [6] and [7]). A recurring observation in all these clinical studies/observations is that reverse remodeling is associated

with an improvement in the clinical manifestations and outcomes in heart failure, raising the interesting possibility that reverse remodeling is linked mechanistically to the observed improved heart failure outcomes.

Although the precise cellular and molecular mechanisms that are responsible for the return toward normal LV size and shape during reverse remodeling are not completely understood, there is a fairly consistent biological theme with respect to the parameters that return toward baseline after pharmacological or device therapy (see the Online Appendix for full citations). As shown in Table 2, there is a series of favorable changes in cardiac myocyte biology, the composition of the myocardium, and the chamber properties of the left ventricle after pharmacological and device therapies that lead to reverse remodeling. With respect to the changes that occur in cardiac myocyte biology, clinical studies of patients undergoing LVAD implantation or cardiac resynchronization therapy have consistently shown a decrease in cardiac myocyte hypertrophy. The morphological changes in cardiac myocyte size are accompanied by changes in gene expression, including reversal of the abnormal fetal gene program, genes involved in sarcomerogenesis, β -adrenergic signaling, the cytoskeleton, and/or return of excitation contraction coupling genes toward expression levels observed in nonfailing hearts in clinical situations in which patients have been treated with beta-blockers, LVADs, cardiac resynchronization therapy, or cardiac contractility modulation. The decrease in cardiac myocyte cell size after LVAD support is accompanied by changes in the proteome as well, including changes in activation and/or activity levels of protein kinases linked to cell growth, including extracellular regulated kinase-1 and -2 and p38, whereas activation/activity levels of Akt and GSK-3 β (a negative regulator of hypertrophy) are unchanged. Treatment with beta-blockers and LVAD support results in decreased hyperphosphorylation of the ryanodine receptor, which has been implicated in a calcium leak from the sarcoplasmic reticulum in failing hearts and hence contractile dysfunction. Normalization of β -adrenergic receptor density and enhanced inotropic responsiveness to isoproterenol have been demonstrated in LVAD-supported failing hearts. Similar findings have been observed after cardiac resynchronization therapy. Last, he-

Table 2 Cellular and Molecular Determinants of Reverse Remodeling

	Beta-Blocker	ACE Inhibitor	ARB	Aldosterone	LVAD	CRT	CSD
Myocyte defects							
Hypertrophy	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased
Fetal gene expression	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased
Myocytolysis	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased
Myocardial defects							
Myocyte apoptosis	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased
MMP activation	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased
LV dilation	Decreased	Stabilized	Stabilized	Stabilized	Decreased	Decreased	Decreased

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CRT = cardiac resynchronization therapy; CSD = cardiac support device; LV = left ventricular; LVAD = left ventricular assist device; MMP = matrix metalloproteinase.

modynamic unloading with LVAD support results in restoration of more normal levels of sarcomeric and cytoskeletal proteins and organization. Collectively, the above genomic and proteomic changes would be expected to lead to functional improvements in the failing cardiac myocyte. Indeed, there is a significant increase in contractility (maximal calcium saturated force generation) in cardiac myocytes isolated from hearts that have undergone LVAD support compared with myocytes isolated before LVAD support.

In addition to the changes in the biology of the adult cardiac myocyte that occur during reverse remodeling, there are a number of important changes that occur within the myocardium, including changes in the ECM and microvascular density (angiogenesis). Intuitively, restoration of ECM content and organization would appear to be critical with respect to facilitating the normalization of LV structure and function after LVAD support. Unfortunately, there is very limited information on this complex topic, and what little information exists is largely phenomenological in nature. Even at the phenomenological level, there was controversy initially concerning the simple question of how total collagen content changes during LVAD support. Some groups reported a decrease in total collagen, whereas other groups reported an increase. One potential resolution to the controversy came with recognition that collagen content decreased in patients taking angiotensin-converting enzyme inhibitors and increased in patients not taking angiotensin-converting enzyme inhibitors, consistent with previous observations that tissue levels of angiotensin II, a profibrotic peptide, were increased in patients supported with LVADs.

Myocardial microvascular density is reduced in heart failure and has been implicated in contractile dysfunction and cardiac remodeling in heart failure. Although morphological and functional data are relatively limited, the extant literature suggests that hemodynamic unloading leads to up-regulation of angiogenesis-related genes and increased microvascular density. However, the functional significance of these findings is unclear given that coronary flow reserve remains impaired after LVAD support.

Finally, improvements in the EDPVR seen with therapies that induce reverse remodeling do not necessarily equate with improvements in all aspects of the complex structure of the ventricular chamber. For example, it has been shown that although significant improvements can be detected in the EDPVR after as little as ~30 days of support, these changes occur without any appreciable change in the chamber radius-to-wall thickness ratio.

Myocardial Recovery

For some etiologies of heart failure, most notably acute lymphocytic myocarditis (8) and peripartum cardiomyopathy (9), spontaneous recovery from heart failure symptomatology and normalization of LV structure and function occur spontaneously in 40% to 50% of patients. Moreover,

similar rates of recovery have been reported for cessation/removal of toxic substances, such as ethanol and anthracyclines, and/or reversal of energetically unfavorable conditions such as tachycardia, transient ischemia, and hyperthyroidism (reviewed in reference [6]). These statements notwithstanding, the natural history of patients undergoing spontaneous myocardial recovery is not at all well characterized. Interestingly, although hemodynamic unloading of the heart in patients with more advanced heart failure leads to reverse remodeling and partial reversal of many aspects of the molecular and cellular heart failure phenotype, the incidence of myocardial recovery is at best ~15% (n = 120) in the selected cohorts of patients that have been reported (Table 3) (Online Appendix) (10,11). Of note, the latest annual report from Interagency Registry for Mechanically Assisted Circulatory Support, which summarized results of 4,366 LVAD recipients from June 2006 to June 2011, reported a 1.4% rate of LVAD explantation for myocardial recovery (12). Thus, although reverse remodeling occurs in the vast majority of patients on prolonged LVAD support and is a *sine qua non* for myocardial recovery, reverse remodeling only rarely results in myocardial recovery. This then raises the important question of why reverse remodeling and myocardial recovery do not have the same clinical outcomes, despite the fact that they involve very similar biological processes.

One potential explanation for this important question comes from a closer inspection of the terminology used to describe these 2 clinical scenarios. The term “reverse remodeling,” as it is currently used, describes the biological process of reversal of the cellular, myocardial, and anatomic abnormalities that occur in the remodeled ventricle. The clinical literature reviewed herein suggests that patients may experience 1 of 2 potential outcomes for this biological process: 1) freedom from future heart failure events and 2) recurrence of heart failure events. Based on these 2 different outcomes of reverse remodeling, we suggest that the term “myocardial recovery” should be used to describe the normalization of the molecular, cellular, myocardial, and LV geometric changes in the heart that provoke cardiac remodeling that allow the heart to maintain preserved LV structure/function in the face of normal and/or perturbed hemodynamic loading conditions (13). Accordingly, myocardial recovery is associated with freedom from future heart failure events. We suggest that the term “myocardial remission” should be used to refer to the normalization of the molecular, cellular, myocardial, and LV geometric changes that provoke cardiac remodeling that are insufficient to prevent the recurrence of heart failure in the face of normal and/or perturbed hemodynamic loading conditions. Thus, although myocardial remission may be associated with stabilization of the clinical course of heart failure as well as reversal of many aspects of the heart failure phenotype, it is not associated with freedom from future heart events.

Are these 2 terms merely semantic or are there potential biological mechanisms that might explain why reverse

Table 3 Outcome Studies on Bridge to Recovery

Study, Year(s)	Design	N	Adjuvant Antiremodeling Drug Protocol	Protocol for Monitoring Cardiac Function	Unloading Duration, Months	Recovery, n (%)		
						Overall	Nonischemic	HF Recurrence/Follow-Up
U.S multicenter, 2007	P	67	Not standardized	Yes	4.5	6 (9)	5 (13.5)	Freedom from death or Tx 100%/6 months
Berlin group, 2008, 2010–2012, 2010	R	188	Not standardized	Yes	4.3	35 (18.6)	35 (18.6)	Freedom from recurrent HF 74% and 66%/3 and 5 yrs, respectively
Harefield group, 2006	P	15	Yes	Yes	10.6	11 (73)	11 (73)	Freedom from recurrent HF 100% and 89%/1 and 4 yrs, respectively
Harefield group, 2011	P	20	Yes	Yes	9.5	12 (60)	12 (60)	Freedom from recurrent HF 83.3%/3 yrs
University of Athens-Harefield group, 2007	P	8	Yes	Yes	6–10	4* (50)	4* (50)	Freedom from recurrent HF 100%/2 yrs
Gothenburg group, 2006	P	18	Not standardized	Yes	6.7	3 (17)	3 (20)	Freedom from recurrent HF or Tx 33%/8 yrs
Pittsburgh group, 2003	R	18	Not standardized	Yes	7.8	6 (33)	5 (38)	Freedom from recurrent HF 67%/1 yr
Osaka group, 2005	R	11	Not standardized	N/A	15.1	5 (45)	5 (45)	Freedom from recurrent HF 100%/8–29 months
Pittsburgh group, 2010	R	102	N/A	N/A	4.9	14 (13.7)	14 (13.7)	Freedom from recurrent HF or death 71.4%/5 yrs
Multicenter, 2001	R	271	N/A	N/A	1.9	22 (8.1)	22 (8.1)	Freedom from recurrent HF or death 77%/3.2 yrs
Columbia group, 1998	R	111	N/A	N/A	6.2	5 (4.5)	4 (8)	Freedom from recurrent HF or death 20%/15 months

*A fifth patient fulfilled recovery criteria (5 of 8, 62.5%) but died of stroke just before left ventricular assist device explantation. Full references for the above studies are provided in the Online Appendix and in reference (20). Modified from Drakos et al. (20).
HF = heart failure; N/A = not available; P = prospective studies; R = retrospective studies; Tx = transplant.

remodeling culminates in 2 distinct clinical outcomes, namely, remission and recovery? Multiple lines of evidence support the point of view that in most instances, reverse remodeling does not lead to a normal heart, despite reversal of many aspects of the heart failure phenotype. First, gene expression profiling studies have shown that only ~5% of genes that are dysregulated in failing hearts revert appreciably to normal after LVAD support, despite typical morphological and functional responses to LVAD support (14,15). Second, although maximal calcium-saturated force generation is improved in myocytes after LVAD support, force generation is still less than in myocytes from nonfailing controls, despite reversal of cardiac myocyte hypertrophy (16). Third, as noted previously, the majority of studies that examined changes in the ECM after LVAD suggested that the ECM does not revert to normal on its own and can actually be characterized by increased myocardial fibrosis. Moreover, our current understanding of changes in the ECM during LVAD support focuses on ECM content and not on the more fundamental issues of its 3-dimensional organization or with the interactions between the collagen matrix and the resident cardiac myocytes, which are likely to be critically important. Fourth, although the LV EDPVRs of LVAD-supported hearts are shifted leftward and overlap those found in nonfailing ventricles, the ratio of LV wall thickness-to-LV wall radius does not return to normal despite normalization of LV chamber geometry (17). Rather, this chamber radius-to-wall thickness ratio remains elevated at nearly twice normal. This has important implications for LV function, insofar as LV wall stress depends critically on this ratio (Laplace's law). Given that end-

diastolic wall stress represents the load on the cardiac myocyte at the onset of systole, the observation that the chamber radius-to-wall thickness ratio is not normalized despite the normalization of LV global chamber properties suggests that the cardiac myocytes in reverse remodeled ventricles are still exposed to increased physiological stresses. Whether this represents loss of functioning cardiac myocytes or failure of the 3-dimensional organization of the ECM to revert to normal is unknown. Thus, the regression of the heart failure phenotype and the accompanying return toward a more normal cardiac phenotype during reverse remodeling does not, in and of itself, signify that the cellular/molecular biology and physiology of these hearts is normal, which may explain why reverse remodeling may be associated with different clinical outcomes.

Are there potential biological differences that may explain the disparate clinical outcomes that occur after reverse remodeling? Although the potential biological differences between myocardial recovery and myocardial remission are not known, there are parallels in mechanical engineering science that may help to illuminate potential important differences as well as to frame future mechanistic discussions. In mechanics, deformation of a material refers to the change in the shape or size of an object due to an applied force. Figure 2A shows an example of a stress versus strain diagram of a material that is exposed to an increased load. With increasing stress, there is an increase in the length of the material until the point when no further changes in length are possible without the material breaking. Importantly, if the material returns to its original state when the load is removed, this is referred to as elastic deformation. In

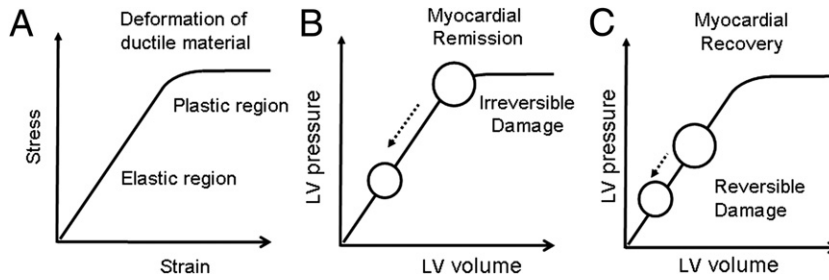


Figure 2 Mechanical Engineering Science and Cardiac Remodeling

(A) Diagram of a stress-strain curve of a ductile material, illustrating the relationship between an applied force (stress) and deformation (strain). Deformation can lead to reversible changes in a material (elastic deformation) if the properties of the material are not changed and irreversible changes in a material (plastic deformation). (B) Hypothetical model of reverse remodeling in a heart that has undergone irreversible damage (plastic deformation). (C) Hypothetical model of reverse remodeling with recovery in a heart that has undergone reversible damage (elastic deformation). LV = left ventricular.

contrast, if during the application of stress the mechanical properties of the material are changed irreversibly, such that the object will return only part way to its original shape when the stress is removed, this is referred to as plastic deformation. It is sometimes the case that elastic deformation occurs under a certain level of stress and plastic deformation occurs when that stress level is exceeded. Regardless, the important distinction is whether the material returns to its original state when the stress is removed. Although precise parallels between cardiac remodeling in heart failure and deformation of solid materials after loading are not appropriate, there could be a heuristic parallel between reverse remodeling and plastic deformation, inasmuch as the reverse remodeled heart does not revert completely to normal after cessation of hemodynamic overloading (Fig. 2B). Although speculative, it is possible that myocardial recovery is more analogous to elastic deformation in that the recovered heart reverts to normal after hemodynamic overloading is removed (Fig. 2C). Thus, we propose that reverse remodeling without recovery represents a reversal of the heart failure phenotype that occurs in hearts that have sustained irreversible damage, whereas myocardial recovery represents a reversal of the heart failure phenotype that occurs in hearts that have reversible damage (Fig. 3). Although the biological motifs that separate reversible (elastic) from irreversible (plastic) changes in the heart are not known, it is likely that the progressive loss of cardiac myocytes, irreversible changes at the DNA level, and the progressive erosion of the native 3-dimensional organization of the ECM surrounding the cardiac myocytes will be critical determinants that distinguish between reverse remodeling and myocardial recovery (5,13). The observation that the great majority of clinical examples of myocardial recovery in the literature occur after transient injury (e.g., viral infection, inflammation, toxic injury) rather than more long-standing and/or permanent injury (e.g., myocardial infarction, genetic abnormalities) is consistent with the point of view that the ability of the heart to “recover” is related to the nature of the inciting injury and the extent of

underlying myocardial damage that occurs during the resolution of cardiac injury. This observation is also consistent with the observation from the LVAD bridge to recovery studies (Table 3), which have consistently shown that recovery is possible in patients with myocarditis and/or postpartum cardiomyopathy, whereas recovery does not occur in patients with irreversible damage from myocardial ischemia/infarction. It is also possible that myocardial recovery may represent a new and unique set of biological adaptations (e.g., changes in integrin signaling and

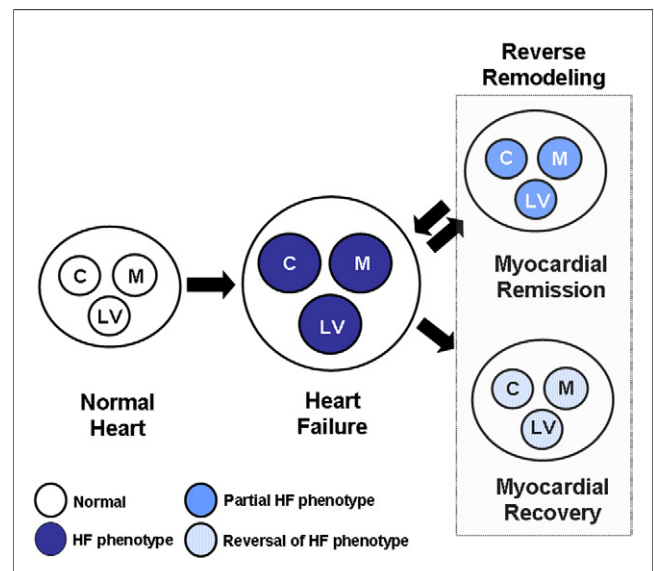


Figure 3 Reverse Remodeling and Myocardial Recovery

Cardiac remodeling arises secondary to abnormalities that arise in the biology of the cardiac myocyte (C), the myocardium (cardiocytes and extracellular matrix [M]), as well as LV geometry, which have collectively been referred to as the heart failure (HF) phenotype. During reverse remodeling, there is a reversal of the abnormalities in the cardiac myocyte as well as the extracellular matrix, leading to a reversal of the abnormalities in left ventricular (LV) geometry. Reverse remodeling can lead to 2 clinical outcomes: 1) myocardial recovery, characterized by freedom from future cardiac events; or 2) myocardial remission, which is characterized by recurrence of heart failure events.

β -adrenergic signaling) that are associated with better pump function and improved prognosis and that these unique adaptations explain the differences between myocardial recovery and remission (6,18,19).

Conclusions and Future Directions

As discussed here, the failing heart is capable of undergoing favorable changes in LV volume and mass and to assume a more normal energetically favorable elliptical shape (reverse remodeling). Although the various components of reverse remodeling have been carefully studied and annotated, it is unclear at present exactly how these changes contribute to restoration of normal LV structure and function. That is, we simply do not understand what the essential biological “drivers” of myocardial recovery are, nor do we understand how they are coordinated. More importantly, we do not understand why reverse remodeling is sometimes associated with freedom from recurrent heart failure events (i.e., myocardial recovery) and why reverse remodeling is sometimes associated with recurrence of heart failure events (5,11). Indeed, the extant literature does not suggest which of the myriad changes that occur during reversal of the heart failure phenotype are most important and/or necessary to preserve LV structure and function in the long term. Here we suggest that reverse remodeling represents a multilevel (molecular, cellular, anatomic) reversal toward a normal myocardial phenotype and that this reversal of phenotype is accompanied by 2 different outcomes, namely, myocardial recovery and myocardial remission. We propose that the difference between these 2 outcomes (Fig. 3) is that myocardial remission represents reversal of the heart failure phenotype superimposed on hearts that have sustained irreversible damage (plastic deformation), whereas myocardial recovery represents reversal of the heart failure phenotype superimposed on hearts that have not sustained irreversible damage (elastic deformation). This formalism, although hypothetical at present, can be validated experimentally and clinically and permits certain predictions with respect to identifying responders and nonresponders to medical and device therapies. For example, one would not expect myocardial recovery to occur in patients with advanced heart failure secondary to ischemic heart disease (Table 3) or even patients with dilated cardiomyopathy secondary to genetic cytoskeletal defects, whereas recovery can be anticipated in appropriately selected subsets of patients with recent-onset heart failure of reversible etiologies (Fig. 1). The quest for elucidating the biological basis for these distinctions extends beyond intellectual curiosity or the need to select appropriate patients for clinical trials. Rather, insights into these distinctions will suggest new heart failure therapies that directly target the phylogenetically conserved pathways that have evolved to repair the myocardium rather than continuing to target signaling pathways that attenuate remodeling. Given our current lack of understanding of the biology of reverse remodeling and

the disparate outcomes of remodeling, it is likely that the learning curve will be extremely steep, now and for the foreseeable future.

Acknowledgments

The authors apologize in advance to our colleagues whose work we were not able to directly cite in this review because of the imposed space limitations. References that were deleted because of space limitations can be found in the [Online Appendix](#). The authors thank Dr. Frank C.P. Yin for helpful discussion regarding the material engineering science concepts that were included in this review.

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Key Words: heart failure ■ left ventricular remodeling ■ myocardial recovery ■ myocardial remission ■ reverse remodeling.

 **APPENDIX**

For a supplemental table and references, please see the online version of this article.