1
Ventricular Remodeling In Ischemic Cardiomyopathy

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1. Introduction

Heart failure in the setting of reduced systolic pump function, if left untreated, is characterized by progressive ventricular dilation and dysfunction. Many of the major advances in pharmacologic treatments for heart failure achieved over the last two decades came with the recognition that this process, referred to as *ventricular remodeling*, results from abnormal mechanical stress on the myocardium (increased preload and afterload) and chronic neurohormonal activation (Figure 1). In the acute setting, loss of myocytes (as during infarction) or a defect of myocardial contraction (e.g., idiopathic cardiomyopathies) reduces overall ventricular pump function. This leads to reduced blood pressure and cardiac output, which activates autonomic reflexes that leads to increased circulating levels of neurohormones. It is believed, on a teleological basis, that these reflexes evolved in order to allow animals to cope with periods of increased energy demand (fight or flight) and to deal with acute blood loss.

In parallel with autonomic reflex activation, decreased systemic blood pressure and flow lead to renal hypoperfusion, which increases aldosterone, renin and angiotensin, I (which leads to angiotensin II) production. In the short term, these factors attempt to restore cardiac output and blood pressure via mechanisms that are considered adaptive. However, if sustained, neurohormonal activation and increased mechanical stresses conspire in a maladaptive process to drive cellular hypertrophy and elongation, global recapitulation of a fetal gene program, myocardial fibrosis, ventricular enlargement and dysfunction, apoptosis[1] and sets up a milieu for dyscoordinated myocardial contraction (e.g., conduction defects) and ventricular arrhythmias. A systemic inflammatory response also has been documented with increases of a multitude of cytokines which are also believed to contribute importantly to myocyte loss and disease progression.[2,3]

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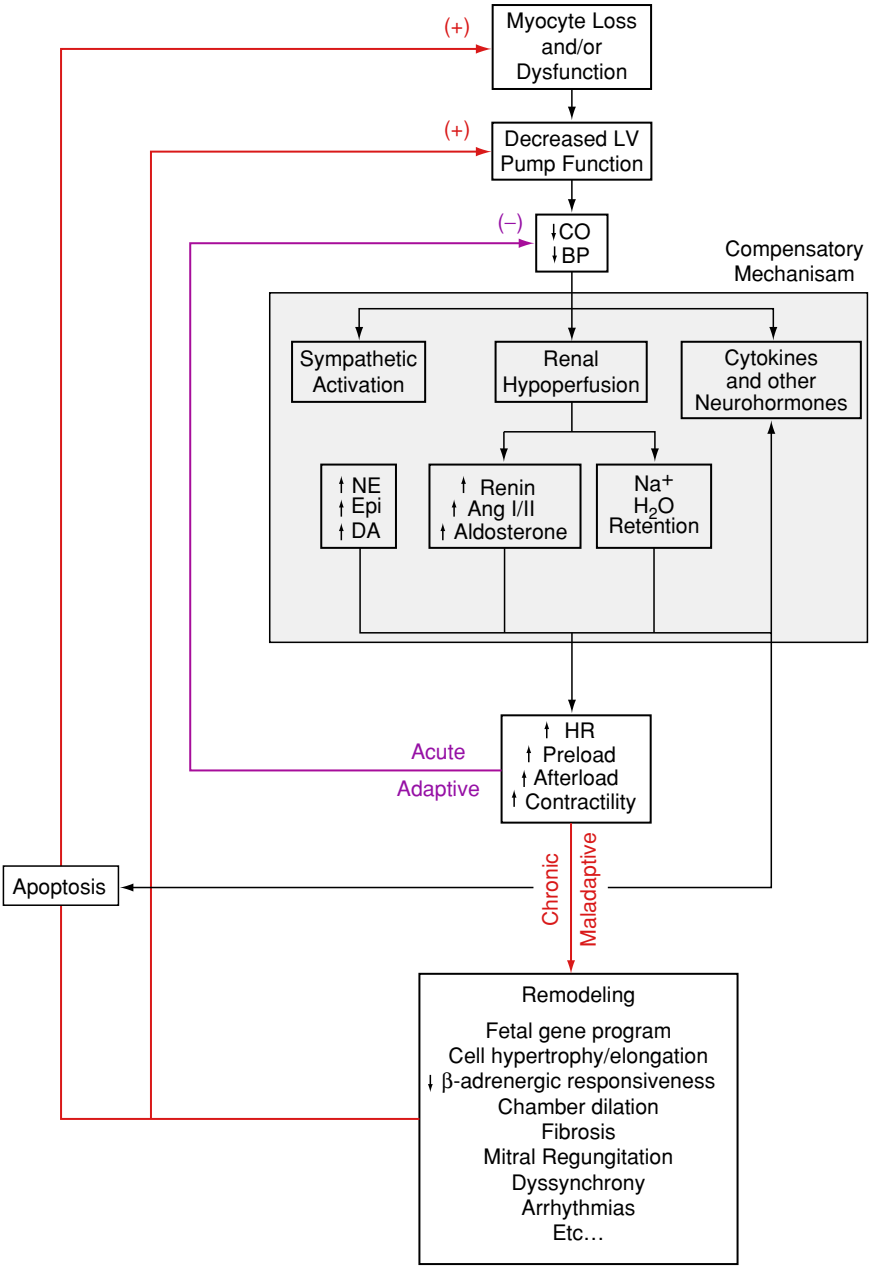

FIGURE 1. The vicious cycle of heart failure

It is now well known that ventricular remodeling involves molecular, biochemical, metabolic, cellular, extracellular matrix and ventricular structural characteristics as well as a multitude of effects on the peripheral circulation and viscera. Importantly, in the post infarct heart, the remodeling process affects not only regions of infarcted myocardium, but also normally perfused myocardium. Indeed, the previously normal myocardium is as affected by remodeling as the infarcted areas and changes in those regions assume a primary role in disease progression. The situation can be even further complicated in ischemic cardiomyopathy because noninfarcted regions can be supplied by stenosed coronary arteries so that active myocardial ischemia can be another factor influencing the remodeling process.

On a structural and functional basis, the remodeling process is readily represented on the ventricular pressure-volume diagram (Figure 2A). Within this framework, systolic and diastolic properties are represented by the end-systolic and end-diastolic pressure-volume relations, (ESPVR and EDPVR, respectively) which define the boundaries within which the normal pressure-volume loop resides (blue). An acute decrease in contractility, as with a myocardial infarction (MI), causes a downward shift of the ESPVR that results in a reduction in stroke volume and blood pressure (red solid line). The acute neurohormonal activation discussed above leads to increased heart rate, arterial and veno-constriction that increase arterial, venous and ventricular end-diastolic pressures (dashed purple line). With sustained neurohormonal activation and its consequences reviewed in Figure 1, the pressure-volume relations gradually shift towards larger volumes. Although stroke volume may be maintained to a large degree, ejection fraction is reduced because of the marked dilation of the left ventricle. In addition, marked myocardial hypertrophy occurs.

The goal of many heart failure treatments, be they pharmacologic, device- or cell-based, is to prevent, slow or reverse this process (Figure 2B). In particular the concept of *reverse remodeling* is an important principle for new treatments of heart failure.

Early experimental work on understanding the process of structural LV remodeling emerged from the studies of Pfeffer and Braunwald using a rat model of myocardial infarction.[4] Rats with induced large MIs underwent a substantially greater degree of chamber dilation over time compared to rats with a small MIs. In these early studies, the degree of chamber dilation was assessed by measurement of the *ex vivo* end-diastolic pressure-volume relationship (EDPVR). Through these studies, the term *ventricular remodeling* became synonymous with a rightward shift towards larger volumes of the EDPVR.

A graphic example of this remodeling process obtained from a canine model of heart failure is shown in Figure 3. A family of pressure-volume loops (obtained during a transient vena caval occlusion) from a normal dog chronically instrumented for measurement of left ventricular pressure (Konigsburg transducer) and ventricular volume (three orthogonally placed sonomicrometer crystals) is shown in Figure 3A. The loops delineate the

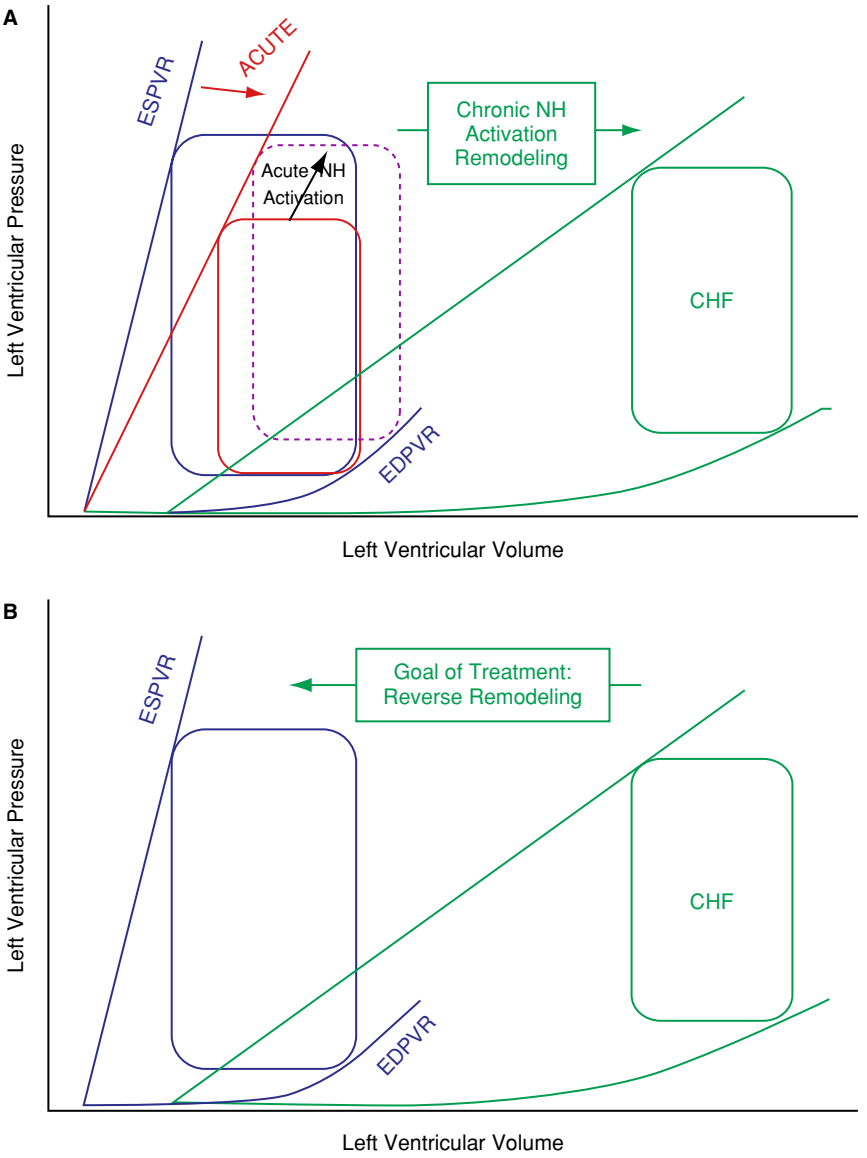

FIGURE 2. A. Changes in end-systolic and end-diastolic pressure-volume relations (ESPVR and EDPVR, respectively) and pressure volume loops with acute ventricular dysfunction (red solid line), with acute autonomic compensation (dashed purple line) and with chronic activation leading to structural ventricular remodeling (green). B. The goal of treatments is to reverse the remodeling process and restore more normal ventricular size, structure and function.

ESPVR and EDPVR. This same animal is then subjected to daily microembolisms via a chronically implanted left anterior descending coronary catheter.[5] Within about 6 to 8 weeks, this procedure induces a state of heart failure, which includes neurohormonal activation, fluid accumulation (ascites, pleural effusions), tachypnea, tachycardia and anorexia. On the pressure-volume plane (Figure 3B), the ESPVR shifts downward indicating reduced systolic performance. It is further seen that the EDPVR shift rightward towards larger volumes and the end-diastolic pressures is increased (arrow). Even after suspension of microembolization, the heart continues to remodel, characterized by further rightward shifts of both ESPVR and EDPVR (Figure 3C) and further elevations of end-diastolic pressure (arrow).

It is postulated that a similar course of events occurs in humans following a myocardial infarction. However, since serial measurements of pressure-volume relations require invasive techniques, it is not possible to delineate so clearly, the remodeling process in a given patient. However, significant insights about a multitude of aspects of ventricular remodeling in humans have been obtained through studies of hearts explanted from patients at the time of orthotopic heart transplant suffering from ischemic cardiomyopathy. Characteristics of these hearts are compared to those of normal human hearts not suitable for transplantation. In addition, studies of explanted hearts obtained from patients who required support with a left ventricular assist device (LVAD) prior to transplantation have provided important information about the extent to which the remodeling process can be reversed. The remainder of this chapter shall review results of these studies.

2. Structural Remodeling in Ischemic Cardiomyopathy

There are several approaches available for studying the remodeling process in humans. Studies in our laboratory have employed the technique of measuring *ex vivo* passive pressure-volume relationships (EDPVRs) from hearts explanted at the time of orthotopic heart transplant; the following discussion will focus on results obtained from ischemic cardiomyopathic hearts. After explantation and preservation with 4°C cardioplegia solution, a compliant water-filled latex balloon is placed into the left ventricular chamber. While measuring pressure within the balloon, volume is varied from a volume adjusted for an intracavitary pressure of 0 mmHg to a volume yielding a pressure of at least 30 mmHg. The pressure-volume point at each volume step is then plotted, resulting in the passive pressure-volume relationship for that heart. Such curves have been obtained from non-failing hearts unsuitable for transplant, hearts explanted from patients with end-stage ischemic heart disease and from hearts that have undergone LVAD support prior to transplant.[7,8] Representative results are shown in Figure 4. Compared to normal hearts (crosses) the EDPVRs of ICM hearts (open circles) were shifted towards significantly larger volumes, a reflection of the gross dilation and

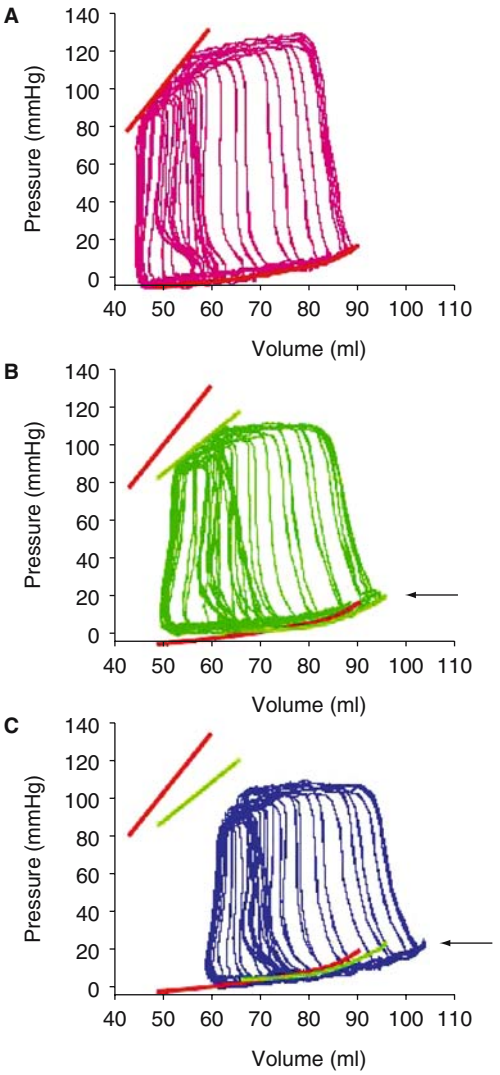

FIGURE 3. Pressure-volume loops obtained during transient vena caval occlusions in a normal dog (A), at the conclusion of an ~8 week period of daily coronary embolizations (B) and after an additional 10 weeks following suspension of embolizations (C). The ESPVR and EDPVR progressively shift towards larger volumes, indicative of remodeling. Once initiated, the remodeling process self propagates even without induction of additional myocardial injury.[6]

structural remodeling that is typical of end-stage cardiomyopathy. In addition, unitless chamber stiffness constant (k, obtained by curve fitting the data to $P=\beta e^{kV/Vw}$ where V_w is volume of the left ventricular wall[9]) is significantly reduced in end-stage ICM hearts compared to normal non-failing hearts.

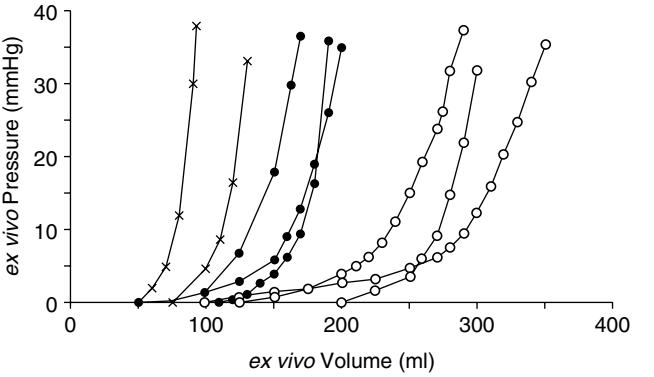

FIGURE 4. Representative left ventricular *ex vivo* pressure volume relationships (EDPVRs) for non-failing (*crosses*), end-stage ischemic heart failure (*open circles*) and LVAD supported ICM hearts (*filled circles*). The structural remodeling process in end-stage ICM leads to a rightward shift of the EDPVRs, but could be reversed following LVAD support.

At the root of these chamber structural changes is frank myocyte hypertrophy and cellular elongation with up to 70% increase in cell volume[10] (Figure 5A and B), increased collagen deposition and increased heart weight (Figure 5C). These changes, in turn, are due to the hemodynamic overload (increased preload and afterload stress) and neurohormonal activation present in these patients.

As late as the 1990's, it was generally believed that when such remodeling was longstanding and severe (such as observed in patients awaiting heart transplant) that these structural abnormalities would be irreversible. Soon after the introduction of LVADs, however, it was appreciated that these abnormalities were not permanent, but could be reversed, at least to some degree.

The primary action of LVADs is to improve cardiac output and blood pressure in terminally ill patients. However, there are several important indirect effects. First, along with normalization of the hemodynamic state comes normalization of the neurohormonal and cytokine milieu.[11] A second indirect benefit of LVADs derives from their anatomic position (withdrawing blood from the LV apex and returning it to the aorta) that results in profound pressure and volume unloading of the left ventricle.[12] Importantly, while the neurohormonal milieu is determined largely (though not entirely) by the blood perfusing the myocardium and is therefore common to the left and right ventricles, the hemodynamic benefits of LVADs are provided only to the left ventricle.[13] Consequently, comparisons of effects on the right and left ventricles further allowed for identification of whether the primary mechanism responsible for reverse remodeling relate to mechanical factors or neurohormonal factors.

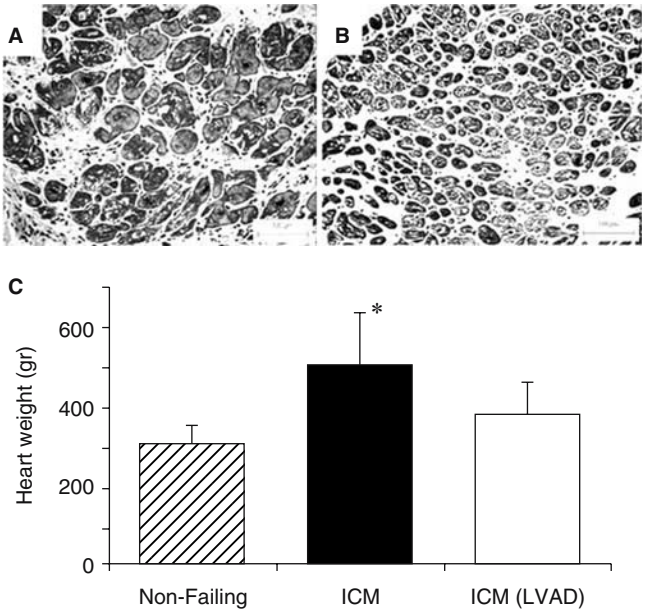

FIGURE 5. Sections of LV free wall demonstrating myocyte hypertrophy in end-stage ischemic cardiomyopathy (A) and following LVAD support (B). Original magnification 10α, Scale bar = 100 μm). (C) Average heart weights from ischemic cardiomyopathic hearts (ICM), ICM hearts following LVAD support, and non-failing heart not used for cardiac transplantation. In end-stage ischemic heart disease heart weight increases tremendously, but could be reverse to almost normal following LVAD support. $^{*}P<0.05$ vs. non-failing and LVAD.

As a consequence of the LVAD support, myocyte hypertrophy and heart mass are significantly reversed (Figure 4 and 5). Similar findings have been reported by Terracciano et al., who found a significant reduction in cell capacitance during LVAD support.[14] Zeifeiridis et al. examined isolated myocytes to evaluate changes in myocyte size and shape after LVAD support and observed a 60% regression of size.[15]

We found that associated with the reduction in cell size and ventricular mass, were significant leftward shifts towards normal of EDPVRs measured in LVAD-supported hearts (Figure 4, filled circles). This observation lead to the concept that the gross structural remodeling of end-stage failing heart could be reversed: *reverse remodeling*.

Interestingly, while the right ventricular EDPVR of patients with end-stage ischemic cardiomyopathy are also shifted towards higher than normal volumes, this relationship is not influenced by LVAD support.[13] This suggests that the primary mechanism of reverse structural remodeling is due to the hemodynamic unloading provided by LVADs, since the RV does not receive the same profound unloading experienced by the LV. Further support for this

concept is derived from the fact that hearts supported by a right ventricular assist device (RVAD) do show RV EDPVR shifts towards lower volumes, similar to what is observed in the LV following LVAD support.[16]

3. Molecular and Cellular Remodeling in Ischemic Cardiomyopathy

The anatomic changes of myocytes that accompanies increased pressure and volume within any heart chamber triggers a sequence of events, some of which are calcium-regulated,[17] that eventually leads to remodeling of individual cells. While physical stretch on the myocardium is believed to be a major regulator of this process, it also involves systemic neurohormones and intracardiac paracrine/autocrine mediators. These individual factors coalesce to produce a cascade of immediate and ultimately prolonged molecular and cellular events mediated in part by altered expression of a variety of genes within both myocytes and non-contractile elements of the myocardium.[18] One of the more widely studied genes is that encoding for the activity of the sarcoplasmic endoreticular calcium-ATPase subtype 2a (SERCA2a) which is known to be down regulated in heart failure. Down regulation of this gene has been linked with transformation of the myocardial force-frequency relationship (FFR). Normally, contractile force increases as contraction frequency is increased and this is referred to as a *positive* FFR. However, in heart failure, contractile force typically declines with increased contraction frequency and this is referred to as a *negative* FFR[19] (see chapter 5, Myocardial contractile performance following MI). In addition, alterations in the expression and/or function of SERCA2a,[20-23] the ryanodine-sensitive calcium release channel (RyR),[24,25] and the sarcolemmal sodium-calcium (Na^+/Ca^{2+}) exchanger[26,27] appear to be associated with various aspects of contractile dysfunction in severe heart failure, although there is some controversy, especially as it relates to changes in Na^+/Ca^{2+} exchanger gene expression. Some studies have indicated that with decreased SERCA2a function in heart failure, a compensatory increase in the activity of the Na^+/Ca^{2+} exchanger occurs as this sarcolemmal protein assumes a greater role in extruding Ca^{2+} during diastole.[19,26,28] Consistent with this process are data indicating up-regulated myocardial expression of Na^+/Ca^{2+} exchanger mRNA in human heart failure.[27] Recent data indicate that levels of Na^+/Ca^{2+} exchanger protein are not necessarily changed in severe human heart failure,[23] and animal studies have suggested that there can be decreased gene expression, and reduced Ca^{2+} flux through the Na^+/Ca^{2+} exchanger in the setting of cardiac failure.[29-31] Our own studies have suggested that Na^+/Ca^{2+} exchanger gene expression is reduced in the heart failure state.

Just as LVAD support has been shown to induce *reverse structural remodeling*, such changes in gene expression associated with heart failure are shown to be reversed following LVAD support: *reverse molecular remodeling*. So, for example, LVAD support has been shown to reverse the abnormalities of

SERCA2a, Na^+/Ca^{2+} and RyR gene expression.[7] In addition, comparison of gene expression of LV and RV myocardial samples it was shown that only LV SERCA2a gene expression and protein content are improved following LVAD support.[13] This suggests that regulation of the expression of these genes is linked with the volume and pressure unloading provided by the LVAD and not with the normalization of neurohormonal milieu. Similar effects are observed in human tissue samples of patients undergoing β-blocker therapy.[32]

While much attention has been given to changes in gene expression, it is increasingly recognized that examination of protein content and function may be more reveling. For example, while it is known that SERCA2a expression is markedly reduced when examined by Northern blot analysis, functional assays of calcium sequestration rates of isolated sarcolemmal vesicles reveals ~75% retention of calcium sequestration capabilities in end-stage heart failure compared to normal controls.[33] Thus, gene expression does not reveal the entire picture. Additionally, post translational modifications of protein function also play a key role in abnormal cell function underlying the pathophysiologic mechanisms of contractile dysfunction. For example, the sarcoplasmic reticular RyR channel, which regulates Ca^{2+} release to the myofilaments, also play a pivotal role in the ability of the SR to store and rapidly release Ca^{2+}.[20] Hyperphosphorylation of RyR in failing human myocardium disrupts the normal coupled gating of neighboring receptors resulting in abnormal ensemble gating patterns, less coordinated SR Ca^{2+} release during excitation, and Ca^{2+} leak during diastole (Figure 6).[25] These abnormalities are reversed during LVAD support.

The abnormalities of cellular properties are too numerous to delineate in this brief review and only a few examples are provided above. It is noteworthy, however, that there are increasing number of reports showing that many molecular, biochemical and cellular abnormalities occurring in the end-stage heart failure can be reversed and/or normalized during LVAD support. The most notable of these include LVAD-induced normalization of β-adrenergic and endothelin-A receptors,[34,35] modulation of antiapoptotic genes,[36] deactivation of nuclear factor-kappaB,[37] normalization of mitochondrial ultrastructure,[38] and down-regulation of matrix metalloproteinases,[39] tumor necrosis factor-α,[40] β-tubulin,[41] and MEK/Erks and Akt/GSK-3.[42]

4. Myocardial Contractile Performance in Ischemic Cardiomyopathy

The molecular, biochemical and cellular remodeling noted in prior sections underlie myocardial contractile dysfunction at rest and in response to different types of stimulation. To study such phenomena, isolated endocardial trabeculae were excised from freshly explanted non-failing and end-stage ischemic cardiomyopathic hearts with and without LVAD support and mounted in a muscle bath connected to a force transducer. Muscles were pro-

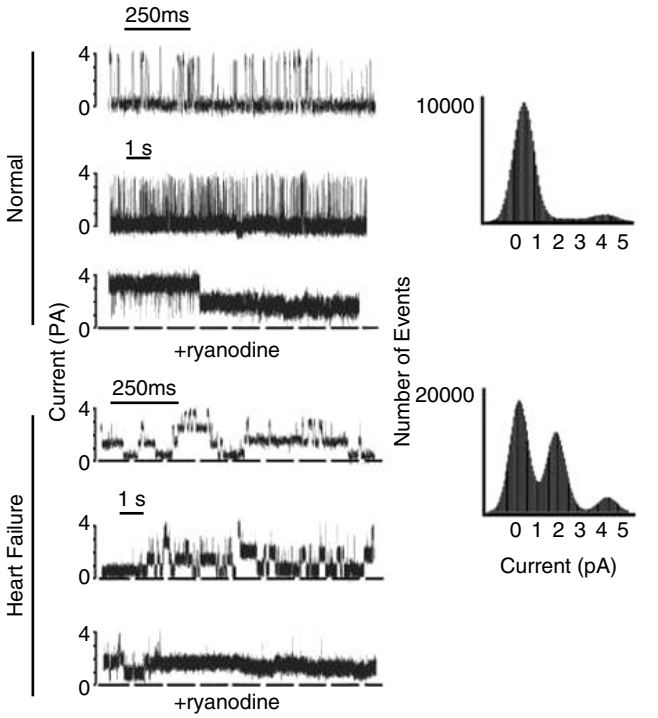

FIGURE 6. Single channel tracings of RyR2 from canine hearts in a non-failing state (top three tracings) and in ischemic cardiomyopathy (bottom three tracings). Corresponding amplitude histograms are at right. The bottom tracing in each set of three shows the characteristics modification of the RyR2 channels by ryanodine (1μM). Recording were at 0 mV.[25]

gressively stretched to the length of maximal force generation (L_{max}). Two separate experiments were performed. The first involved exploration of contractile response to increased rate of stimulation (the force-frequency relationship, FFR) and the second was a test of myocardial contractile response to β-adrenergic stimulation (isoproterenol, 1 μM).

For studies of FFR, stimulation frequency was initially set at 1 Hz and then increased at 0.5 Hz increments to a maximum of 3 Hz (Figure 7). At 1 Hz stimulation frequency, developed force generation of non-failing, ICM and LVAD supported hearts (normalized to cross-sectional area) were similar to each other. However, at higher rates of stimulation force increased in the normal myocardium (positive FFR) but declined in trabeculae from ICM hearts (negative FFR). As discussed above, this phenomenon is believed to be the result of the changes in expression and function of proteins involved with calcium cycling (e.g., SERCA2a).[7,13,26,43-45] In LVAD supported hearts, however, the positive FFR was restored. Interestingly, and paralleling the changes in

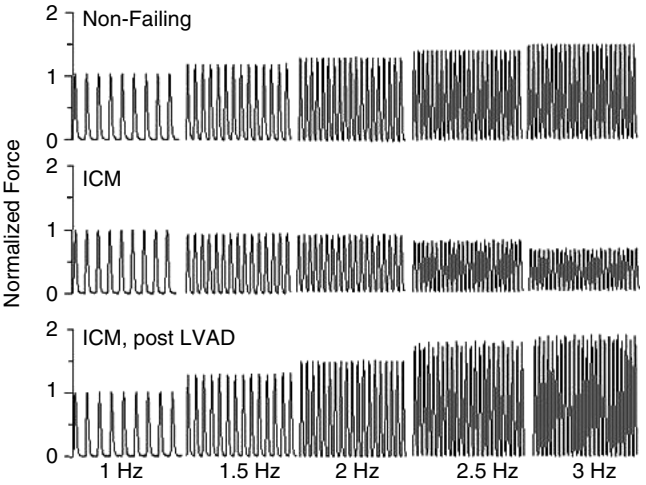

FIGURE 7. Representative force tracings from isometrically contracting trabeculae isolated from a non-failing and two ICM hearts with and without LVAD support. A positive FFR is evident following mechanical unloading. Bar=5 sec.

SERCA2a expression, FFR of the remodeled RV myocardium was also negative and did not revert to a positive FFR following LVAD support.[13]

Myocardial contractile force exhibited a blunted responsiveness to β-adrenergic stimulation in the failing, remodeling LV myocardium (Figure 8).[46] Concomitant with LVAD-induced normalization of β-adrenergic receptor density and phosphorylation of RyR calcium release channel, this response was significantly improved (Figure 8). In comparison to the FFR, however, β-adrenergic responsiveness is restored not only in the unloaded LV but also in the RV. This paralleled comparable recovery of β-adrenergic receptor density and RyR phosphorylation in both ventricles.[25]

5. Pharmacologic Therapies and Other Devices also Induce Reverse Remodeling

With regard to reversal of remodeling, the present chapter focused on the effects of LVADs. It is clear that the degree and breadth of remodeling observed during LVAD support is far greater than with any other treatment investigated thus far, it is important to note that use of other devices and pharmacologic agents can also reverse remodel the failing heart, though to a lesser degree.

For example, experimental and clinical studies have clearly indicated that drugs such as angiotensin converting enzyme inhibitors and β-blockers can prevent or reverse structural and perhaps molecular remodeling in the setting

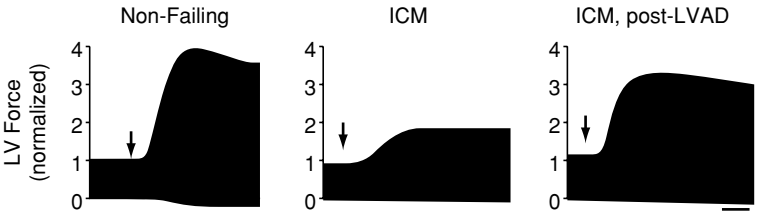

FIGURE 8. Representative continuous force tracings during exposure to isoproterenol (1 μM, arrow). The response from ICM is blunted, while LVAD supported hearts show a strong response similar to non-failing hearts. Scale bar=20 sec.

of heart failure.[47,48] Angiotensin converting enzyme inhibitors exert direct effects on ventricular preload and afterload as well as effects on the neurohormonal system and were shown to improve clinical outcome and LV function.[49,50] In addition, there are several potential mechanism of benefit from β-blockade in heart failure. At the tissue level experimental studies have provided insights into molecular and cellular mechanism contributing to prevention and/or reversal of remodeling by reducing apoptosis,[51] collagen deposition and myocyte hypertrophy.[52]

Similarly, devices such as a passive myocardial wrap[53] and cardiac resynchronization therapy[54] have also been associated with varying degrees of reversal of cardiac dilation and normalization of gene expression.

6. The Challenge: Reverse Remodeling by Cell Therapy

There are three major problems with the use of LVADs to induce reverse remodeling. First is that in a vast majority of patients the degree of recovery, though on average vastly greater than achieved with pharmacologic agents, is insufficient to permit removal of the device.[55,56] Second, in cases when devices are removed, the reverse remodeling is not permanent, and the hearts remodel again once required to support the circulation.[55-57] Third, currently available LVADs are extremely invasive and associated with high morbidity and mortality.[58] Their use will therefore be limited to the vast minority of critically ill, end-stage heart failure patients. Thus, current LVADs provide proof of the concept that sufficient mechanical unloading and normalization of neurohormones and cytokines can improve LV function, but new technologies will be needed to optimize and take advantage of this remarkable property of the myocardium in order to more substantially help greater numbers of patients with debilitating symptoms.

Accordingly, many technologies are currently being investigated. One such class of technology is cell-based therapies such as the use of stem cells, progenitor cells and autologous myoblasts to repopulate infarcted regions of ischemic cardiomyopathic hearts.[59] There are many challenges that need to be

overcome in order to arrive at a successful cell therapy for heart failure (Figure 9). The challenge begins with choosing a suitable cell to be used. Many different types are being investigated, each with its own theoretical advantages and disadvantages. Independent of type, sufficient quantities of the cell need to be made available. In patients with ischemic cardiomyopathy it is possible that as much as 40-50% of the original myocyte number is lost, which would amount to as myocardial masses in the range of 40 to 60 grams of tissue. Thus, even if the goal were to replace a relatively small fraction of lost myocardium there is a need to either develop means of producing and injecting large quantities of cells or to establish an environment that will allow proliferation of cells once they take up residence. In either case, the cells need to engraft, which may require disruption of the dense collagen scar present in infarcted areas. In order to ensure long-term survival, the cells need to be appropriately nourished so a vascular supply needs to be generated. The energetic cost of meaningful contraction is high and would need to be supported by aerobic metabolism. In order to most effectively contribute to contraction the engrafted cells need to be activated in synchrony with the native myocardium. This could be achieved either by formation of electrical connects between the graft and native myocardium (which would typically involve generation of gap junctions), by artificial pacing of the graft, or pos-

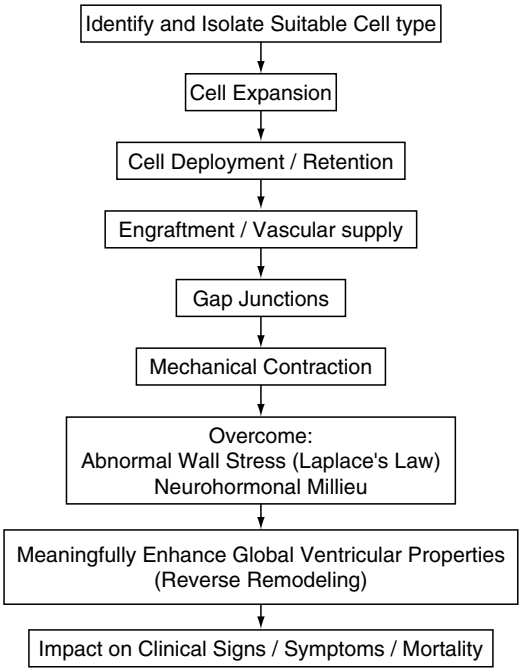

FIGURE 9. Summary of the milestones that need to be achieved in order to arrive at a successful cell therapy for heart failure. See text for details.

sibly via a mechanism whereby mechanical stretch created by the native myocardium could activate the engrafted cells. The engrafted cells would be then required to contract. For this, formation of myofilaments in an organized manner is required along with all necessary regulatory proteins (tropoinin, tropomyosin, etc) and control mechanisms for calcium handling. Due to the preexistent disease state, these cells are engrafted into a hostile environment. According to Laplace's Law (pressure is proportional to wall stress divided by radius of curvature: $P \propto \sigma/r$) the cells are placed at a mechanical disadvantage so that there is less efficient transformation of the force they generate into ventricular pressure. The high stress state may unfavorable affect the cells. Similarly, the neurohormonal milieu into which they are placed is in many ways cytotoxic and may induce undesirable effects on cellular function. Despite these factors, the cells must contract to a sufficient degree to meaningfully influence global ventricular performance. Ultimately, it must be demonstrated that these effects on function translate to beneficial effects on patient symptoms, quality of life and longevity.

The discussion above is predicated on the assumption that indeed the goal of cell-based therapies is to repopulate the infarcted heart with cells that contract and contribute to contraction. However, this assumption is not universally accepted as a requirement for a successful treatment. Some advocate that it would be sufficient that by as yet unspecified mechanisms, injected cells may favorably influence properties of the scar and induce beneficial effects on ventricular structure which in the long run may induce reverse remodeling of other aspects of myocardial structure and function. Our own preliminary studies in an animal model of ischemic cardiomyopathy suggest that autologous skeletal myoblasts injections, whether via a surgical procedure or during a catheter-based percutaneous procedure, are associated with reverse structural remodeling as evidenced by shifts of the end-systolic and end-diastolic pressure-volume relationships back towards lower, more normal volumes. This was observed even though we were unable to identify any significant regions of cell engraftment in the injection regions.

7. Summary and Conclusions

Profound cardiac remodeling occurs in the setting of ischemic cardiomyopathy, which affects all regions of the heart, independent of whether a particular region is infracted, ischemic or normally perfused. The impact is broad, affecting molecular, biochemical, metabolic, cellular and structural aspects of the myocardium. This process is driven by increased mechanical stresses, in the form of increased preload and afterload, as well as abnormally elevated levels of cytokines and neurohormones. With respect to a majority of myocardial characteristics that undergo remodeling, the process appears to be similar in ischemic and non-ischemic cardiomyopathies, although in ischemic cardiomyopathic hearts there are the added factors of massive cell

loss and regions of dense scar. Until the early 1990's it was commonly held that the end-stage failing heart was irreversibly dilated, hypertrophic and dysfunctional. Early clues from studies of pharmacologic neurohormonal blockade (specifically angiotensin II converting enzyme inhibitors and later β-blockers) indicated that the process could be slowed, halted and perhaps reversed. Following the introduction of LVADs, however, it because clear that almost every aspect of remodeling could be reversed. The only characteristic which does not seem to normalize during LVAD support relates to the extracellular matrix[39,60,61] which exhibits enhanced collagen turnover and interstitial fibrosis.

The precise mechanisms underlying the various aspects of remodeling and reverse remodeling remain to be determined. The mechanisms underlying hypertrophy and chamber remodeling in response to pressure and volume loading of the myocardium involve intricately orchestrated up- and down-regulations of a multitude of intracellular signaling cascades and post-translational modifications. Although having been investigated for over 40 years, these mechanisms are still not fully understood. It has been our working hypothesis that reverse remodeling involves the same mechanisms working in the opposite direction. Hopefully, future research will provide precise answers that will allow development of new treatments to achieve the same profound effects on reverse remodeling as LVADs. It is postulated that cell-based therapies may achieve this goal. The questions to be addressed broadly in this book are whether one or more cell types exist that can be injected into a heart with ischemic cardiomyopathy that can, by one mechanism or another, reverse remodel the grossly dilated heart and improve ventricular function to such a degree that will alleviate symptoms of heart failure and prolong life.

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