Dynamic Regulation of the Extracellular Matrix After Mechanical Unloading of the Failing Human Heart

Recovering the Missing Link in Left Ventricular Remodeling

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One of the most exciting scientific challenges that faces investigators in the field of heart failure today is to unravel the mechanisms that are responsible for preventing and/or reversing the process of left ventricular (LV) remodeling (dilation) in the failing heart. Given that LV remodeling may contribute to disease progression in heart failure and that all drugs that have been shown to exert beneficial effects on mortality in patients with heart failure also favorably impact the remodeling process, it is likely that the quest to identify the mechanisms responsible for reversing LV remodeling will lead to the identification of novel therapeutic targets for the treatment of heart failure. Thus far, clinical studies with β-blockers and left ventricular assist devices (LVADs) have consistently shown that these 2 treatment modalities allow the heart to become smaller and to assume a more normal prolate ellipsoid geometry, thus increasing the mechanical efficiency of the heart. However, it is not at all intuitively obvious how or why this occurs. Moreover, although considerable research time and effort has been expended on understanding the basic mechanisms that promote LV dilation, it is not clear that a simple reversal of these same mechanisms will allow the heart to revert back to its normal size and shape. Thus, our understanding of the mechanisms that are responsible for the regression of LV remodeling remains far from complete.

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The clinical experience with LVADs has yielded a number of unique insights into the mechanisms of the LV remodeling, the most notable of which have clustered around the important changes that occur in the biology of the failing human cardiac myocyte. Studies performed with clinical material obtained before and after LVAD support have demonstrated favorable changes in myocyte structure (decreased size, decreased myocytolysis) and function (increased contractility). These changes in myocyte biology have been accompanied by improved sarcoplasmic reticular handling of calcium and upregulation of the gene transcripts for proteins that regulate calcium handling. On the basis of the such studies, the general perception has been that changes in the biology of the myocyte are the driving force behind the regression of LV remodeling that occurs after LVAD support. In the present issue of Circulation, Li et al report that LVAD support results in decreased activation of collagenolytic enzymes, referred to as matrix metalloproteinases (MMPs), and in an increase the natural inhibitors of MMPs, the tissue inhibitors of matrix metalloproteinases (TIMPs). These studies, which were performed in the same patient using paired myocardial samples obtained before and after LVAD implantation, also show that there was an increase in the ratio of un-denatured/total collagen, which is an indirect measure of the amount of cross-linking of the collagen network. The latter findings suggest (but do not prove) that mechanical unloading of the heart in some way allowed the extracellular matrix to become reorganized.

The findings by Li and colleagues are important for 2 reasons. One is that these studies are the first clinical studies to demonstrate clearly the dynamic nature of the components of the extracellular matrix in response to mechanical unloading of the failing heart. The second, even more important finding is the suggestion that changes in collagen volume/structure may facilitate the reversal of LV dilation that has been observed after LVAD support. Thus, these provocative studies by Li et al challenge the prevailing dogma that the regression of LV remodeling occurs entirely as the result of changes in the biology of the adult cardiac myocyte. However, to place the studies by Li and colleagues into proper perspective, it is helpful to digress for a moment and discuss what is known about the regulation of the extracellular matrix in the failing heart.

Alterations in the Extracellular Matrix in the Failing Heart

The alterations that occur in the extracellular matrix of the failing human heart can be categorized broadly into changes in the volume, composition, and organization of the extracellular matrix. Two basic morphologically distinct patterns of myocardial collagen accumulation (fibrosis) exist based on the alignment of thick and thin collagen fibers to one another and to cardiac muscle. Perhaps the most widely recognized alteration in the extracellular matrix is the development of perivascular fibrosis around intramyocardial blood vessels. A second form of fibrosis, termed “replacement fibrosis,” involves the excessive deposition of fibrillar collagen that occurs between individual cardiac myocyte bundles. Replace-
ment fibrosis is thought to occur after the death of myocytes. Studies in failing human myocardium have shown that there is a quantitative increase in collagens I, III, VI, and IV, fibronectin, laminin, and vimentin, and that the ratio of type I collagen to type III collagen is decreased in patients with ischemic cardiomyopathy. The increased fibrous tissue would be expected to lead to increased myocardial stiffness, which would presumably result in decreased myocardial shortening for a given degree of afterload. Moreover, clinical studies suggest that there is a progressive loss of cross-linking of collagen in the failing heart and a loss of connectivity of the collagen network with individual myocytes. Loss of appropriate collagen cross-linking would be expected to result in profound alterations in LV structure and function. For example, mice with a genetic defect in the cross-linking of collagen (Mo) have an impaired ability to generate myocardial force. Further, loss of cross-linking of fibrillar collagen has been associated with progressive LV dilation after myocardial injury. Thus, both the amount and the organization of the collagen content are important determinants of myocardial structure and function in the failing heart.

Until recently, the deposition of collagen in the failing heart was regarded as a simple additive process, with progressive collagen deposition accumulating as a function of time. However, a number of recent studies (Table) have suggested that regulation of the extracellular matrix is a dynamic process and that the failing heart is continually subjected to ongoing collagen synthesis and collagen breakdown, consistent with the concept that mammalian cells continuously make and degrade constituent and functional proteins. Indeed, it has been estimated that the heart "regenerates" itself over a period of 3 weeks. Recent studies have shown that a portfolio of MMPs are activated within the failing myocardium (Table). Conceptually, progressive activation of MMPs might be expected to lead to progressive disruption of the organization of the collagen network that supports the arrangement of myofibrillar bundles within the heart and allows the heart to contract in a synchronized manner. Disruption of the extracellular matrix would be expected to lead to LV dilation as a result of mural realignment ("slippage") of myocyte bundles and/or individual myocytes within the LV wall and to LV dysfunction as a result of dysynchronous contraction of the LV. Thus, disruption of the extracellular matrix would be expected to lead to mural realignment (slippage) of myocyte bundles and/or individual myocytes within the LV wall, thus facilitating LV dilation, and to engender the development of asynchronous myocardial contractions, thus producing LV dysfunction.

However, the biology of matrix remodeling in heart failure is likely to be much more complex than the simple presence or absence of MMP activation, insofar as the degradation of the matrix is also controlled by glycoproteins termed TIMPs, which are capable of regulating the activation of MMPs by binding to and preventing these enzymes from degrading the collagen matrix of the heart. Nonetheless, the exact role of TIMPs in the failing heart is far from clear, insofar as it seems that under certain conditions TIMPs may actually stabilize and/or localize MMPs, which in turn may facilitate the activation of MMPs. Moreover, the extant literature does not suggest a clear-cut pattern of TIMP expression in the failing heart, with both increased and decreased TIMP levels reported. Nonetheless, when viewed together, the above observations suggest that the alterations in collagen volume and collagen organization contribute directly to the remodeling process and that the changes in the extracellular matrix are likely to be extremely dynamic, reflecting the complex interplay between MMP activation and TIMP expression.

Conclusions

The findings by Li et al in this issue of Circulation clearly demonstrate the plasticity of the extracellular matrix after mechanical unloading of the failing heart. Importantly, the changes in MMP activity after LVAD support were accompanied by increased collagen cross-linking in the failing hearts, suggesting that the decrease in MMP-induced collagenolytic activity allowed for repair and/or reorganization of the fibrillar collagen component of the extracellular matrix. Given that organization of the fibrillar collagen network is important in terms of regulating LV structure and function, the studies by Li and colleagues suggest the important possibility that changes in the organization of myocardial collagen may in some way contribute to the decrease in LV chamber size that has been observed after LVAD support. How this occurs and why this occurs is still somewhat of a mystery.

One possibility is that changes in the biology of the cardiac myocyte (contractility) occur pari passu with the reorganization of the collagen network, with the result that as myocardial function improves and LV end-systolic and end-diastolic volumes decrease, the collagen network becomes progressively reorganized around a smaller LV chamber. However, it bears emphasis that this explanation is completely speculative and that our understanding of the biological underpinnings of the regression of LV remodeling is embryonic at present. As with most studies in the field of heart failure, the explanation for this phenomenon is likely to be somewhat different from...
our original expectations. This statement notwithstanding, the insightful studies by Li et al\(^\text{10}\) suggest that reorganization of the collagen network will likely play an important role in this process.

**Acknowledgments**

This article was supported by research funds from the National Institutes of Health (P50 HL-O6H, RO1 HL58081-01, RO1 HL61543-01, HL-42250-10/10, and RO1 HLJAG 61483) and from the American Heart Association, National Center. The authors thank Mary Helen Soliz for secretarial assistance and Dr Andrew I. Schafer for his past and present support and guidance.

**References**


**Key Words:** Editorials ■ heart diseases ■ remodeling ■ heart failure ■ surgery
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Circulation. 2001;104:1089-1091

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