The Pathologic Basis of Recovery

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KEYWORDS

• Reverse remodeling • Left ventricular assist device • Unloading left ventricle

KEY POINTS

- Hearts supported by ventricular assist device pumps demonstrate reverse remodeling caused by unloading of the left ventricle.
- The unloading mechanisms are associated with morphologic, functional, and molecular effects.
- The morphologic changes in unloaded hearts include (1) regression of myocyte diameter, volume, and length; (2) increase in interstitial fibrosis; (3) increase in the inflammatory and side population cells; (4) increase in interstitial microneovascularization.
- These profound structural and molecular modifications are opening new frontiers in the understanding of recovery mechanisms, reverse remodeling, and improvisation in the use of left ventricular assist devices as destination therapy and bridge to recovery.

INTRODUCTION

In patients with end-stage heart failure (HF), heart transplantation (HTx) continues to be the choice of treatment. HTx offers a substantial survival benefit, with 10-year survival of greater than 50% in comparison with a similar survival at the end of 1 year in patients with advanced HF.[1] However, as HTx is not feasible in all candidates because of age, comorbidities, and the limited number of donors,[2,3] there is increasing demand for left ventricular assist devices (LVADs) as a bridge to transplantation. LVADs have also been successfully deployed as a bridge to complete recovery and as a destination therapy.[4] The change from pulsatile-flow to continuous-flow assistance and the resulting miniaturization of the device have been associated with (1) an improvement in LVAD durability and decreased need for pump replacement; (2) a reduction in complications including bleeding and infections; and (3) improved survival and quality of life.[5]

Reverse remodeling resulting from unloading of the left ventricle is accompanied by a favorable change in the morphologic, functional, and molecular characteristics of the myocardium.[6] The morphologic changes observed in reverse-remodeled hearts involve myocytes, interstitial spaces, interstitial cells, and intramural vessels. Because most LVADs to date have been a bridge to heart

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transplantation, pathologic studies have been performed in paired samples from the same patients, namely the left ventricular (LV) apex obtained at LVAD implantation and the heart excised at transplantation.[7]

CHANGES IN THE MYOCARDIAL COMPARTMENT

Myocyte Size

Histopathologic changes in unloaded left ventricles have been investigated since the early clinical studies of LVADs,[7] and have demonstrated different results ranging from myocyte hypertrophy following LVAD implantation to myocyte atrophy.[8–11] In isolated cardiac myocyte preparations from patients with congestive HF, a 50%, 48%, and 20% increase in measured cell volume, length, and diameter, respectively, has been reported; on the other hand, LVAD treatment for 75 $\pm$ 5 days resulted in a 28% reduction of cell volume, 20% reduction of length and diameter, and 36% reduction of myocyte area. In unloaded hearts in vivo, even though morphometric studies demonstrate that the myocytes may be smaller,[12] a significant decrease in diameter occurs only in subendocardial myocytes[13–15] and, even when smaller, the observed values remain within normal limits for myocytes.[16,17] In animal models, however, long-term unloading has induced cardiomyocyte atrophy or a decrease in myocyte size beyond the normal range.[14,18]

Myocyte Membranes

Information about the integrity of the myocyte sarcolemma has been obtained from conventional light and electron microscopy studies, and from immunostaining of cell membrane proteins such as dystrophin. It has been shown that the LV myocardium of patients with end-stage cardiomyopathy, independent of cause, shows selective abnormality of the N-terminus of dystrophin.[19] However, chronic mechanical unloading with a pulsatile-type LVAD results in normalization of dystrophin expression, implicating dystrophin itself in the progression of ventricular dysfunction.[19] Similar improvement in dystrophin expression has also been documented in the right ventricle by both pulsatile and continuous-flow LVAD.[20]

Myocyte Nuclei

Understanding reverse remodeling in unloaded ventricles is additionally provided by the study of the morphology and number of single-nucleated and binucleated myocyte nuclei, as well as DNA content before and after LVAD support. After unloading, the number of polyploid myocytes and myocyte DNA content decreased while the number of binucleated myocytes was noted to increase, which suggests reverse remodeling of the myocyte structure and function in unloaded ventricles.[21] There was a substantial decrease in myocardial DNA content, and a decrease in polyploid cardiomyocytes from 40% to 25%. On the other hand, a significant increase was observed in diploid cardiomyocytes from 35% to 50% and in binucleated cardiomyocytes from 5% to 10% after unloading.[21] The latter increase in diploidy in post-LVAD samples alludes to a possible progression through the cell cycle with mitosis or by increase in stem-cell activity.[21] It has been hypothesized that migration and/or proliferation of stem cells in the myocardium could result in a net gain of diploid/binucleated cardiomyocytes, endothelial cells, or vascular smooth muscle cells.[22] The heart contains a reservoir of stem cells and progenitor cells with diverse expression of numerous cell markers such as c-kit/CD117, Sca-1, MDR-1, and islet-1.

Table 1
Summary of current knowledge on morphologic changes in unloaded hearts

Morphologic	Left Ventricle: Morphologic Phenotype of Unloaded Hearts
Myocyte hypertrophy	Regression
Myocyte diameter	Decrease
Myocyte nuclei	Decrease
Myocyte length (isolated myocytes)	Decrease
Myocyte volume (isolated myocytes)	Decrease
Ploidy in myocytes	Decrease
Myocyte DNA	Decrease
Binucleated myocytes	Increase
Myocyte membrane markers (dystrophin)	Dystrophin expression restored
Interstitial fibrosis	Increases
Inflammatory cells	Increase
Side cells	Increase
Small vessels	Increase
Endothelial cell markers	Increased expression of makers of endothelial activation