Molecular Basis of Recovering on Mechanical Circulatory Support

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KEYWORDS

- Reverse remodeling • Molecular mechanisms • Advanced heart failure
- Mechanical circulatory support

KEY POINTS

- The goal of developing a molecular/cellular profile to predict responders to left ventricular assist device (LVAD) support as a bridge to recovery in patients with heart failure (HF) will be important and complementary to clinical parameters to help identify and target this patient population.
- Our insights into different system levels of mechanisms by LVAD support are increasing and suggest a complex regulatory system of overlapping biological processes.
- To develop novel decision-making strategies and patient selection criteria, HF and reverse cardiac remodeling will be conceptualized and explored by a multifaceted research strategy of transcriptomics, metabolomics, proteomics, molecular biology, and bioinformatics.
- Knowledge of the molecular mechanisms of reverse cardiac remodeling is in its early stages, and comprehensive reconstruction of the underlying networks is necessary.

INTRODUCTION

The number of patients with heart failure (HF) is increasing. In 2010, 6.6 million US adults 18 years of age or older (2.8%) had HF. In 2008, 1 in 9 death certificates (281,437 deaths) in the United States mentioned HF. It is estimated that by 2030, an additional 3 million people will have HF, a 25.0% increase in prevalence from 2010. HF contributes to more than 250,000 deaths a year, results in 2.4 to 3.5 million hospitalizations a year, 12 million to 15 million outpatient office visits a year, and total costs estimated at 39.2 billion dollars a year.[1] The prevalence of advanced HF (AdHF), constituting between 1% and 10% of the population with HF, is estimated to total between 30,000 and 300,000 patients in the United States. From a regional HF care perspective, for example, in the Greater Los Angeles area with a population of more than 10,000,000, the prevalence of HF is estimated at more than 100,000 people, and those with AdHF at more than 10,000 people. AdHF carries a prognosis similar to cancer.

Over the past decade, mechanical circulatory support device (MCSD) therapy has been beneficial as a bridge to cardiac transplantation, and anecdotal evidence suggests that patients with HF with mechanical assist devices experience direct cardiac benefits. Moreover, recent trials on

The authors have nothing to disclose.
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Heart Failure Clin 10 (2014) S57–S62
http://dx.doi.org/10.1016/j.hfc.2013.08.007

limited numbers and subpopulations of patients (notably REMATCH [Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure]) support earlier observations of improved cardiac function and point toward the use of assist devices as destination therapy. Therefore, the role of long-term MCSD is increasing and gaining importance relative to heart transplantation.[2] To investigate mechanisms of myocardial recovery during long-term MCSD, the National Heart, Lung, and Blood Institute convened the working group Recovery from Heart Failure with Circulatory Assist. The team included cardiac surgeons, cardiologists, and experts in experimental research. The goal was to prioritize recommendations to guide future programs in: (1) elucidating the mechanisms leading to reverse remodeling associated with a left ventricular assist device (LVAD); (2) exploring advanced treatments, including novel pharmacologies, tissue engineering, and cell therapies, to optimize recovery with LVAD therapy; and (3) identifying target genes, proteins, and cellular pathways to focus on production of novel therapies for myocardial recovery and cardiovascular disease. The working group also made research and clinical recommendations to translate findings into improved therapeutic strategies and device design: (1) support collaborations among clinical and basic scientists with an emphasis on clinical/translational research, which might lead to clinical trials; (2) identify candidate patients most likely to benefit from LVAD as a destination therapy; (3) explore potential biomarkers indicating when patients could most successfully be weaned from devices; and (4) promote clinical and experimental study of mechanically assisted organs and the tissue derived from them.[3] In this review, the data that have accrued over the past decade on molecular mechanisms of recovery during mechanical circulatory support are summarized and evaluated.

STAGED HF INTERVENTIONS ASSOCIATED WITH MULTILEVEL REVERSE REMODELING

Lifestyle changes such as moderate endurance training and continuous positive airway pressure therapy in patients with HF with sleep apnea induce reverse remodeling. Therapies aimed at neurohormonal blockade, also termed neurohormonal modulation therapy, such as angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and aldosterone antagonists improve organ level markers for reverse remodeling, including ejection fraction, ventricular volumes, and mass. For β-blockers, reverse molecular remodeling was also shown in biopsy specimens on the cellular and subcellular level. Aldosterone has a central role in promoting cardiac fibrosis which may be partially independent of angiotensin II, because it has also been shown in animal models, humans, and isolated cardiac fibroblasts exposed to aldosterone.[4] Hence, an aldosterone antagonist may be antifibrotic. Cardiac resynchronization therapy improves exercise capacity and quality of life in patients with ventricular dyssynchrony and is associated with geometric and functional reverse remodeling over time. Surgical approaches for reverse remodeling, such as mitral valve replacement, aneurysmectomy, and volume reduction have been developed, but may also be associated with high perioperative mortality. More recent methods under exploration include percutaneous approaches to ventricular partitioning of dysfunctional segments. Mechanical unloading of the failing ventricles by LVADs induces well-characterized reverse remodeling on the cellular and subcellular level. Whether this reverse remodeling translates into sustained organ recovery and patient survival remains to be shown.[5] This article focuses on the systematic review of molecular evidence of reverse remodeling related to the key domains of heart functions (ie, structural maintenance, systemic neuroimmunoendocrine regulation, muscle mechanics [contraction/relaxation], electrophysiology, perfusion, and energy metabolism).

REVERSE REMODELING OF STRUCTURAL BIOLOGY

Several histology studies analyzing the morphology and size of cardiomyocytes in patients with HF supported by LVAD described a strong decrease of cell volume, cell profile area, and cell length. These effects in HF were more profound in the most distorted areas and strongly correlated with the duration of LVAD support. Mechanical unloading of the ventricle has also shown a reversal of cardiomyocyte damage by reduction of necrosis, contraction bands, and myocytolysis. LVAD support also induces normalization of cardiac sarcomeric proteins, vinculin, desmin, and tubulin. Whether and to what extent interstitial connective tissue deposits can be reversed after LVAD support is still a matter of dispute, with several contradicting reports to date.[6–9]

The Harefield group reported a seminal experience using clenbuterol. A total of 15 patients with nonischemic cardiomyopathy who required LVAD implantation were studied; 6 recovered sufficiently to allow explantation of the device compared with 9 who did not recover and required transplantation. Left ventricular myocardial samples were