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TRANSLATIONAL PERSPECTIVES

Advancing the Science of Myocardial Recovery With Mechanical Circulatory Support

A Working Group of the National, Heart, Lung, and Blood Institute

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SUMMARY

The medical burden of heart failure (HF) has spurred interest in clinicians and scientists to develop therapies to restore the function of a failing heart. To advance this agenda, the National Heart, Lung, and Blood Institute (NHLBI) convened a Working Group of experts from June 2 to 3, 2016, in Bethesda, Maryland, to develop NHLBI recommendations aimed at advancing the science of cardiac recovery in the setting of mechanical circulatory support (MCS). MCS devices effectively reduce volume and pressure overload that drives the cycle of progressive myocardial dysfunction, thereby triggering structural and functional reverse remodeling. Research in this field could be innovative in many ways, and the Working Group specifically discussed opportunities associated with genome-phenome systems biology approaches; genetic epidemiology; bioinformatics and precision medicine at the population level; advanced imaging modalities, including molecular and metabolic imaging; and the development of minimally invasive surgical and percutaneous bioengineering approaches. These new avenues of investigations could lead to new treatments that target phylogenetically conserved pathways involved in cardiac reparative mechanisms. A central point that emerged from the NHLBI Working Group meeting was that the lessons learned from the MCS investigational setting can be extrapolated to the broader HF population. With the precedents set by the significant effect of studies of other well-controlled and tractable subsets on larger populations, such as the genetic work in both cancer and cardiovascular disease, the work to improve our understanding of cardiac recovery and resilience in MCS patients could be transformational for the greater HF population. (J Am Coll Cardiol Basic Trans Science 2017;2:335–40)

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The enormous medical burden of heart failure (HF) (1) combined with the scientific challenge to defy biological limits, has spurred interest in clinicians and scientists to restore the function of a failing heart. To advance this agenda, the National Heart, Lung, and Blood Institute (NHLBI) convened a Working Group of experts from June 2 to 3, 2016, in Bethesda, Maryland. The charge of this group was to develop recommendations for the NHLBI that will advance the science of cardiac recovery in the setting of mechanical circulatory support (MCS), to enhance its realization as a therapeutic intervention, and to promote sustained cardiac recovery. Of note, this scientific agenda may yield advances in MCS device design and management that could reduce MCS-associated adverse events and favorably affect the phenomenon of cardiac recovery.

Previously, perceptions held that the heart possessed limited ability to recover in response to significant injury. However, clinical practice has demonstrated important examples of cardiac plasticity (i.e., reverse myocardial remodeling) in a variety of clinical scenarios either occurring spontaneously (e.g., acute myocarditis) or facilitated through intervention (e.g., treatment of tachycardia-induced cardiomyopathy, pharmacological-directed therapy, or cardiac resynchronization therapy) (2,3). With advanced stages of the disease, clinical experience suggests the notion that chronic mechanical unloading of the heart with ventricular assist devices (VADs) can favorably influence the complex process of reverse cardiac remodeling, such that patients placed on long-term MCS can achieve variable degrees of improvement in the structure and function of the native heart along with reversal of the systemic HF phenotype (4–6).

Excess pressure and volume load drives the cycle of progressive myocardial dysfunction and cardiac remodeling in chronic HF (7). VADs provide significant volume and pressure unloading and increased cardiac output, which allows a reversal of stress-related compensatory responses of the overloaded myocardium. As a result, some patients placed on long-term MCS demonstrate reverse cardiac remodeling with restoration of cardiac function, permitting weaning from the MCS device. **Table 1** summarizes the results of key clinical outcome studies investigating cardiac functional and structural improvement following long-term MCS therapy (only prospective studies were included) (8–20). The differences in cardiac recovery rates in these studies likely represents variability in study design, patient selection, and differing acceptable thresholds of cardiac recovery to permit device explantation, as defined by the investigators. Recently, 2 prospective observational studies have reported on the prevalence of cardiac recovery with MCS therapy. The ongoing North American multicenter trial (RESTAGE-HF [Remission From Stage D Heart Failure]) announced promising preliminary results: 12 of 36 (33%) patients with advanced nonischemic dilated cardiomyopathy (<5 years of HF history) reached the study pre-defined explant criteria and underwent MCS device explantation (21). The primary endpoint of this study is freedom from MCS or heart transplantation 1 year post-VAD explant. The trial completed its planned enrollment of 40 patients and expects to announce its full results at the end of 2017. The Utah Cardiac Recovery Program reported on 154 patients with chronic advanced dilated cardiomyopathy supported with a continuous flow left VAD (acute HF was prospectively excluded by study design) and observed an improvement in left ventricular ejection fraction of ≥40% in 21% of patients with nonischemic cardiomyopathy and 5% in those with ischemic cardiomyopathy (11). Of note, as evident in **Table 1**, the latter cardiac recovery results in ischemic and nonischemic chronic dilated cardiomyopathy are consistent with earlier conclusions published by the Berlin, US LVAD, Montefiore, Gothenburg, and Vancouver groups (8–14).

Understanding the mechanisms of cardiac recovery following MCS may be paramount to facilitating cardiac recovery in the broader HF population. Unlike other established medical HF therapies that lead to significant cardiac improvements, MCS therapy offers a unique scientific paradigm to permit studies of the human myocardium from tissue samples obtained both at the time of MCS device implant and following the intervention with MCS at the time of device explant (either due to cardiac recovery or due to heart transplantation) (**Figure 1**). This special investigational setting provides an unparalleled opportunity to perform in-depth characterizations of recovery signatures at the clinical, physiological, cellular, and molecular levels in humans or in animal models designed to simulate the clinical use of MCS devices. As depicted in **Figure 1**, results from such studies could lead to rational therapeutic approaches to facilitate cardiac recovery in the various etiologies and stages of HF.

The NHLBI Working Group identified a critical shortcoming in the field of cardiac recovery with MCS in that most studies to date have failed to correlate functional outcomes with molecular, cellular, or histological findings (4–6). As a result, these earlier studies provide limited information on whether