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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ABSTRACT

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 Thorac Cardiovasc Surg* 2017;154:165-70)

MCS viewed as a "research vehicle" that could help advance the science of cardiac recovery.

Central Message

The NHLBI convened a Working Group of experts to develop recommendations aimed at advancing the science of cardiac recovery in the setting of MCS and advanced HF.

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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 (ie, reverse myocardial remodeling) in a variety of clinical scenarios either occurring spontaneously (eg, acute myocarditis) or facilitated through intervention (eg, 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

TABLE 1. Prospective studies investigating cardiac functional and structural improvement during chronic left ventricular assist device support

Group, year, reference	n	HF etiology	Adjuvant drug therapy protocol	Heart function monitoring protocol	LVAD support duration (mo)	Cardiac recovery*	Freedom from HF recurrence after explantation, follow-up duration
US LVAD Working Group, 2007 ⁸	67	NICM: 55% ICM: 45%	Not standardized	Yes	4.5	NICM: 13.5% ICM: 3.3%	100%, 6 mo
Berlin, 2008 and 2010 ^{9,10}	188	NICM: 100%	Not standardized	Yes	4	NICM: 19%	74% and 66%, 3 and 5 y, respectively
Utah Cardiac Recovery Program, 2016 ¹¹	154	NICM: 60% ICM: 40%	Not standardized	Yes	6	NICM: 21% ICM: 5%	N/A
Montefiore, 2013 ¹²	21	NICM: 62% ICM: 38%	Yes	Yes	9	NICM: 23% ICM: 0%	100%, 57 mo
Gothenburg, 2006 ¹³	18	NICM: 83% ICM: 17%	Not standardized	Yes	7	NICM: 17% ICM: 0%	33%, 8 y
Vancouver, 2011 ¹⁴	17	Not reported	Not standardized	Yes	7	NICM and ICM: 23%	100%, 2 y
Pittsburgh, 2003 ¹⁵	18	NICM: 72% ICM: 28%	Not standardized	Yes	8	NICM: 38% ICM: 20%	67%, 16.5 mo
Texas Heart Institute, 2003 ¹⁶	16	NICM: 75% ICM: 25%	Yes	Yes	8	NICM: 58% ICM: 50%	78%, 14.3 mo
US IMAC, 2012 ¹⁷	14	NICM: 100%†	Not standardized	Yes	3.5	NICM: 67%	87.5%, 17.5 mo
Harefield, 2006 ¹⁸	15	NICM: 100%	Yes	Yes	11	NICM: 73%	100% and 89%, 1 and 4 y, respectively
Harefield, 2011 ¹⁹	20	NICM: 100%	Yes	Yes	9	NICM: 60%	83%, 3 y
University of Athens, 2007 ²⁰	8	NICM: 100%	Yes	Yes	7	NICM: 50%	100%, 2 y

HF, Heart failure; LVAD, left ventricular assist device; NICM, nonischemic cardiomyopathy; ICM, ischemic cardiomyopathy; N/A, not applicable. *"Cardiac recovery" was defined in all studies but the Utah Cardiac Recovery study as LVAD explantation due to cardiac functional and structural improvement (degree of improvement and specific criteria varied between studies). In the Utah Cardiac Recovery study,¹¹ "cardiac recovery" was defined as post-LVAD left ventricular ejection fraction $\geq 40\%$ in at least 2 consecutive turn-down echocardiograms and no left ventricular ejection fraction $<40\%$ at later time points (independently of whether the device was eventually explanted). Despite the heterogeneity in the study design, it seems that most programs (Berlin, US LVAD Working Group, Montefiore, Gothenburg, Vancouver, and Utah groups) identified significant cardiac functional and structural improvement in 15% to 25% of NICM and 4% to 5% of ICM. †The US IMAC (Intervention in Myocarditis and Acute Cardiomyopathy) study group¹⁷ included only patients with "recent onset cardiomyopathy."

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 $\geq 40\%$ 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 observed biological changes occurring during the period of MCS therapy could be associated with true cardiac recovery mechanisms or alternatively represent epiphenomena related to the MCS therapy, but not directly related to reverse cardiac remodeling. Examination of tissue from patients with various degrees of MCS-induced myocardial functional recovery (ie, “responders”) and from MCS patients without functional myocardial improvement (ie, “nonresponders”) is critical. Thus, combined functional and biological studies represent a sound approach to begin distinguishing between these 2 scenarios: True mechanistic insights versus epiphenomena.²²⁻²⁹ Future, in-depth, investigational steps incorporating a rigorous basic science scientific approach could assign causality and lead to the discovery of novel therapeutic targets.

Extrapolating the lessons learned from the MCS investigational setting to the broader HF population was a central point that emerged from the NHLBI Working Group meeting (Figure 1). 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,³⁰⁻³³ the work to improve our understanding of cardiac recovery and resilience in MCS patients could be transformational for the greater HF population (Figure 1). Research in this field could be innovative in many ways, and Working Group members 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 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 rather than perpetuating current approaches of targeting pathways that attenuate adverse remodeling.³ They also have the potential to change the paradigm in the treatment of chronic HF from one of attenuation of adverse cardiac remodeling to induction of self-repair mechanisms in specific patient populations, and to revise the existing dogma that severe HF requiring MCS support always indicates end-stage, nonreversible,

FIGURE 1. The MCS investigational setting is a unique transformative “research vehicle” that could help advance the science of cardiac recovery, HF reversal, and MCS innovation. MCS, Mechanical circulatory support; HF, heart failure; LV, left ventricle; MVR, mitral valve replacement/repair; AVR, aortic valve replacement/repair; CRT, cardiac resynchronization; RAAS, renin-angiotensin-aldosterone system.

myocardial disease.³⁴⁻³⁶ With these possibilities in mind, the Working Group made the following *recommendations* (and specific examples for each) to the NHLBI regarding areas of need and opportunity in the science and engineering of cardiac recovery associated with MCS³⁷:

1. Explore mechanistic approaches at the genetic, molecular, cellular, microstructural, or physiological level to improve the understanding of myocardial recovery and develop novel interventions.

- a. Assess the incidence, completeness, and sustainability of recovery using integrated physiology.
- b. Determine and exploit the mechanistic link between alterations in MCS pressure-volume loading profiles associated with myocardial recovery (ie, identify and optimize biomechanical loading regimens that predict or contribute to sustained myocardial recovery).
- c. Develop methodologies to follow and optimize sustained recovery in post-explant patients, including novel imaging and sensor technologies.
- d. Identify associations between molecular, hematological, and/or biochemical markers and hemodynamic/clinical parameters that: (1) define clinical recovery; or (2) define maladaptive consequences during MCS.
- e. Interrogate genetic/genomic responses in recovery that may be relevant to the broader HF population.

2. Utilize epidemiological approaches and population-based studies to identify the associative host factors and MCS device characteristics that influence the incidence and degree of myocardial recovery associated with MCS.

- a. Distinguish between favorable and unfavorable host factors that affect recovery with MCS (ie, age, sex, genetics, disease state, duration of HF, and so on).
- b. Identify the biological and clinical determinants of the degree and sustainability of recovery.
- c. Assess the degree and sustainability of recovery in HF populations receiving MCS and non-MCS interventions.
- d. Determine favorable and unfavorable device characteristics or clinical events related to devices that influence myocardial recovery (eg, unloading characteristics, flow characteristics, the effect of MCS adverse events on recovery, and understanding MCS effects on the cardiovascular system to reduce them).

3. Leverage innovative strategies and approaches to investigate the science and engineering of myocardial recovery with MCS.

- a. Develop appropriate animal models for targeted mechanistic studies of myocardial recovery.

- b. Develop objective measures of unloading and reloading of myocardium using advanced imaging modalities and sensors, metabolic techniques, and physiological data.
- c. Develop novel MCS device designs and control strategies that could enhance myocardial recovery.
- d. Develop a bio-repository to implement high priority recommendations.
- e. Leverage existing networks (ie, data sources such as clinical registries) to implement translational and/or clinical studies of recovery.
- f. Develop specialized expertise and infrastructure for pre-clinical testing of novel adjunctive therapies to promote myocardial recovery.
- g. Translate novel adjuvant interventions (shown in pre-clinical studies or human lab-based studies to enhance recovery) into clinical therapies through randomized clinical trials or other novel adaptive trial designs.

The previously mentioned recommendations tie very well with the NHLBI objectives, as described in the recently released new NHLBI strategic vision,³⁸ and especially understanding resilience, identifying factors that account for individual differences in pathobiology and in responses to treatment, and developing and optimizing novel therapeutic strategies to treat and cure disease. The Working Group also recommended inclusion of both adult and pediatric populations. Future research efforts may also include patient-reported outcomes and cost data to allow for study of interventions aimed at recovery on quality-of-life and cost-effectiveness.

Finally, the Working Group also developed the following *working definition of cardiac recovery*: “A reversal of the pathological state of the myocardium with significant improvement in cardiac structure and function sufficient to achieve a sustained remission from recurrent heart failure events.”

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APPENDIX

For supplemental tables, please see the online version of this article.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support. The views expressed in this article are those of the authors and do not necessarily represent those of the National Institutes of Health or the US Department of Health and Human Services.

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