Consensus Statement

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 on June 2–3, 2016, in Bethesda, Maryland, to develop recommendations for the NHLBI aimed at advancing the science of cardiac recovery in the setting of mechanical circulatory support (MCS). MSC 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 developing 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 impact 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 Cardiac Fail 2017;23:416–421*)

Key Words: Cardiac remodeling, mechanical circulatory support, myocardial recovery, ventricular assist devices.

The enormous medical burden of heart failure (HF),[1] combined with the scientific challenge to defy biologic 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 on June 2–3, 2016, in Bethesda, Maryland. The charge of this group was to develop recommendations for the NHLBI that will advance the science

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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 occurring either spontaneously (eg, acute myocarditis) or facilitated through intervention (eg, treatment of tachycardia-induced cardiomyopathy, pharmacological-directed therapy, 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, two prospective observational studies have reported on the prevalence of cardiac recovery with MCS therapy. The ongoing North American multicenter trial (Remission From Stage D Heart Failure [RESTAGE-HF]) announced promising preliminary results: 12 of 36 (33%) patients with advanced nonischemic dilated cardiomyopathy (<5 years of HF history) reached the study predefined explant criteria

Table 1. Prospective Studies Investigating Cardiac Functional and Structural Improvement During Chronic Left Ventricular Assist Device (LVAD) Support

Group, Year	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%/3 y; 66%/5 y
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%/1 y; 89%/4 y
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; ICM, ischemic cardiomyopathy; N/A, not applicable; NICM, nonischemic cardiomyopathy.

*"Cardiac recovery" was defined in all of the studies except the Utah Cardiac Recovery study as LVAD explantation owing 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 ≥40% in ≥2 consecutive turn-down echocardiograms and no LVEF <40% at later time points (independently from whether the device was eventually explanted). Despite heterogeneity in study design, it appears that most programs (Berlin, US LVAD Working Group, Montefiore, Gothenburg, Vancouver, and Utah groups) identified significant cardiac functional and structural improvement in 15%–25% of NICM and 4–5% of ICM.

†The US IMAC (Intervention in Myocarditis and Acute Cardiomyopathy) study group[17] included only patients with "recent-onset cardiomyopathy."