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PERSPECTIVE

Clinical myocardial recovery during long-term mechanical support in advanced heart failure: Insights into moving the field forward

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Myocardial remodeling induced by pressure and volume overload drives the vicious cycle of progressive myocardial dysfunction in chronic heart failure (HF). Mechanical volume and pressure unloading induced by implantable cardiac assist devices allows a reversal of stress-related compensatory responses of the overloaded myocardium so that selected patients requiring long-term mechanical circulatory support for advanced HF can achieve clinically meaningful degrees of improvement in the structure and function of their native heart. Insights from clinical and translational studies on myocardial recovery with mechanical circulatory support may enhance the understanding of how the pathophysiologic mechanisms of HF progression might be reversed. The end points of ongoing and future translational and clinical studies are discussed to identify specific investigational strategies that may advance the field of myocardial recovery driven by hemodynamic unloading of the heart.

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The classically held view that the human heart has limited ability to recover after a variety of insults has been challenged by the occurrence of cardiac function improvement observed in clinical practice such as that seen with acute myocarditis or restoration of cardiac performance by the use of guidelines-directed medical therapy.[1,2] Furthermore, selected patients requiring left ventricular (LV) assist devices (LVADs) due to advanced HF have experienced sufficient myocardial improvement as a result of hemodynamic rest that they were able to be weaned from mechanical circulatory support (MCS). It is hypothesized that LVADs effectively reduce myocardial volume and pressure overload, thereby triggering structural and functional reverse remodeling.[3,4] This perspective reviews the current state of the field of hemodynamically facilitated myocardial recovery, and the challenges faced to achieve progress in this are discussed.

Clinical cardiac recovery during mechanical unloading is real

Prospective vs retrospective studies

Figure 1 summarizes the key findings of prospective (Figure 1A) and retrospective (Figure 1B) investigations on myocardial recovery driven by the mechanical unloading provided by LVADs.[5–20] The myocardial recovery rates, defined as myocardial functional improvement sufficient to permit withdrawal of MCS, are highly variable. Notably the lowest myocardial recovery rates occur in retrospective studies, and the highest are reported from studies prospectively aimed at inducing recovery with specific protocols applied to carefully selected patients. Although most prospective bridge-to-recovery (BTR) MCS studies (Figure 1A) included protocols to serially measure myocardial function, the frequency of assessment and reloading/exercise conditions were highly variable. Similarly, the definition of myocardial recovery and LVAD explant criteria lacked consistency. Importantly, only 2 groups (Harefield- Athens recovery group and Montefiore group)

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Table 1 Ventricular Assist Device Weaning Assessment Protocols[6,7,13–15,21–23]

- Stage 1—Screening phase: serial cardiac structural and functional evaluation (suggested duration 6–12 months)
  - Serial echocardiography
    - Monthly or Bimonthly
    - Full VAD support and minimal VAD support for 15–30 minutes
  - Patients revealing favorable findings (e.g., LVEF > 40%–45%, LVEDd < 60 mm) proceed to Stage 2
- Stage 2—Weaning phase
  - Exercise capacity testing and hemodynamic evaluation
    - Right heart catheterization: full and minimal VAD support for 15–30 min
    - Exercise capacity and myocardial reserve (6-Minute Walk Test, or cardiopulmonary exercise test or dobutamine stress test): minimal VAD support
  - VAD explantation criteria: structure, function, and hemodynamics (values at minimal VAD support and/or peak exercise)
    - Echocardiogram
      - LVEDd < 60 mm
      - LVESd < 50 mm
      - LVEF > 45%
    - Right heart catheterization
      - PCWP <15 mm Hg
      - CI > 2.4 liters/min/m^2
    - Cardiopulmonary exercise test
      - V_{O_2} max > 16 ml/kg/min
      - V_E/V_{CO_2} < 40

CI, cardiac index; LVEDd, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESd, left ventricular end systolic diameter; PCWP, pulmonary capillary wedge pressure; VE/VCO_2, slope of ventilation versus carbon dioxide production; VO_2max, maximal oxygen consumption; VAD, ventricular assist device.

used a standardized aggressive adjuvant neurohormonal blockade drug protocol.[13–16] Table 1 summarizes the practical aspects of the main BTR protocols reported thus far.[6,7,13–15,21–23]

A universal factor across studies that explains the variability in results reported is the diversity of the populations included in their propensity for recovery. Studies that included mostly non-ischemic cardiomyopathy patients found higher rates of myocardial recovery,[5,13–15] and higher recovery rates were observed in patients with shorter duration of HF (i.e., shorter than 1 to 2 years).[6,12–14] With US Intervention in Myocarditis and Acute Cardiomyopathy[12] and the study from the United States LVAD working group,[7] most of the HF patients included in the prospective studies summarized in Figure 1A were HF patients with advanced chronic cardiomyopathy and dilated ventricles and not patients with acute HF caused by acute myocarditis or other acute etiologies that have a higher propensity for spontaneous cardiac recovery even without any disease-modifying interventions.

Two ongoing prospective efforts recently announced promising interim results. The Utah Cardiac Recovery Program reported its prospective experience with serial echocardiograms in patients with chronic advanced dilated cardiomyopathies unloaded with continuous-flow VADs (acute HF cases prospectively excluded by study design) and found that 19% of the patients that completed at least a 6-month period of mechanical unloading achieved a final LVEF of $\geq$40%.[22] Also, the ongoing North American multicenter prospective Remission From Stage D Heart Failure (RESTAGE-HF) investigating VAD BTR in chronic non-ischemic cardiomyopathy patients recently also announced promising preliminary results at the ISHLT 35th Annual Meeting.[23] Of 20 patients who completed adequate follow-up, 5 (25%) have reached the study pre-defined explant criteria and have been successfully explanted after a support duration of 265 days (range, 197–417 days). On the basis of current recruitment rates, the trial is expected to complete its enrollment of 40 patients in early 2016. The patient population of this multicenter trial is restricted to individuals with a non-ischemic HF and enrollment within 5 years of HF onset to select those patients most likely to achieve improvement of cardiac function from hemodynamic unloading provided by the LVAD on top of background high-dose anti-neurohormonal therapy.

Compared with the prospective studies, the myocardial recovery rates were low in the retrospective studies (Figure 1B).[17–20] The major study design limitations leading to underestimation of the myocardial recovery rate in the retrospective BTR studies include (1) lack of protocols to serially assess the function of the mechanically unloaded heart, (2) absence of guidelines on the use of adjuvant anti-remodeling pharmacologic therapy that may have synergistic effects with hemodynamic unloading, and (3) lack of standardization of criteria for VAD explantation and definition of myocardial recovery. However, despite these limitations, the observation that recovery rates are likely to be higher in non-ischemic cardiomyopathy with a shorter duration of HF history has been first identified in these retrospective studies.

Post hoc queries of VAD multicenter registries and trials

Multicenter VAD trials and registries, such as Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS),[24–26] were designed to examine primarily real-world classical indications such as bridge-to-transplantation (BTT) and destination therapy (DT). As a consequence, the 3 specific limitations mentioned in the prior paragraph were magnified in reports derived from these registries and trials. Most of the centers included in those reports did not have active VAD BTR research programs due to other research priorities in these institutions. In most advanced HF centers for a BTT or DT patient who is doing well as an outpatient, clinicians usually do not focus on the potential for cardiac recovery unless the patient is experiencing a serious VAD complication (e.g., pump thrombosis, infection, etc.) in hopes of a potential device explantation. Therefore, most centers report recovery rates