Letters to the Editor

Left Ventricular Assist Devices in Chronic Heart Failure

More Questions Than Answers?

We welcome the paper by Drakos et al. (1), who investigated the longitudinal effects of continuous-flow left ventricular assist device (LVAD) unloading on cardiac structure and function. The authors concluded that younger patients and those with earlier LVAD implantation since onset of heart failure achieved the largest structural improvements and the most favorable functional recovery (1). Nonetheless, the report raises more questions than those it purports to address.

First, neither the paper nor the supplementary material describes which devices were actually used as LVADs. As each device has its own unique characteristics and risk–benefit profile that may translate on the individual response to cardiac unloading (2), we recommend that the authors provide comparative data testing whether any specific device was associated with better or worse results than the others.

Second, it is well established that several pathophysiological mechanisms interplay in a complex, yet hitherto incompletely determined, fashion with the benefits of LVAD. Specifically, important mediators in the recovery of cardiac function after LVAD implantation should include proapoptotic genes such as caspases; microribonucleic acid; tumor necrosis factor-α, with its essential regulation of maladaptive cardiac remodeling; and insulin-like growth factor-1 (3,4). Furthermore, the demonstration that cardiomyocytes are not terminally differentiated cells with the capacity to re-enter the cell cycle even in LVAD models strongly suggests that they might also be involved in determining which patients do or do not respond favorably to LVAD therapy in routine clinical practice (5–7).

However, no comprehensive and unified appraisal of the aforementioned pathophysiological mechanisms has been performed before in a suitably large cohort of subjects treated with LVAD support. We thus believe that it is crucial to further investigate the cluster of metabolic, neuroendocrine, and molecular markers and chemokines for a "full biomolecular profile" of patients receiving LVAD (8), which is expected to provide a more precise diagnostic and prognostic tool to guide the choice and timing of LVAD implantation as well as to monitor the impact of LVAD on cardiac remodeling and recovery well after its deployment. Indeed, the precise characterization and modulation of molecular pathways and resident stem cells would allow the optimization of left ventricular response aiming for a more satisfactory cardiac recovery.

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Reply

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We appreciate the interest that Dr. Marullo and colleagues have taken in our study (1). Previous data on left ventricular assist device (LVAD)-induced myocardial recovery have suggested that the patient's age and duration of heart failure history may be associated with successful recovery (2,3). In our study, patients who achieved a meaningful functional and structural myocardial recovery were younger (median age 48 years) and had a shorter duration of heart failure symptoms (median 1 year), agreeing with such observations. Comparative studies between pulsatile and continuous flow devices have shown differences in the degree of left ventricular (LV) unloading, hemodynamic profile, and their potential to induce myocardial recovery, as we have recently summarized (4). However, such hemodynamic disparities are not apparent among different types of the continuous-flow LVAD (5), which was the type of device evaluated in our study. The assist devices implanted in our study included 57 (71%) HeartMate II (Thoratec, Pleasanton, California), 10 (13%) HVAD (HeartWare International,

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Framingham, Massachusetts), 6 (7%) Jarvik 2000 (Jarvik Heart, New York, New York), 5 (6%) VentrAssist (Ventracor Ltd, Chatswood, NSW, Australia), and 2 (3%) Levacor (WorldHeart, Salt Lake City, Utah) LVADs. There were no significant differences in the degree of LV unloading, specifically right atrial pressure ($p = 0.76$), mean pulmonary artery pressure ($p = 0.20$), pulmonary vascular resistance ($p = 0.40$), pulmonary capillary wedge pressure ($p = 0.33$), and cardiac index ($p = 0.26$), among the various types of devices (overall p value was obtained by Kruskal-Wallis test). Similarly, when examining the distribution of patients who achieved an LV ejection fraction $\geq$40%, we found no significant difference between individual device types ($p = 0.12$).

We agree that diverse and complex pathophysiological mechanisms might be responsible for the structural and functional benefits observed with LVAD unloading. We have recently summarized information from various groups, including our own, that examined the effects of LVAD unloading on calcium cycling, contractile function, metabolism and bioenergetics, beta-adrenergic signaling, cytokines, cytoskeletal proteins, fibrosis, myocyte hypertrophy, and gene expression (4). However, due to the limited data correlating structure and function, it is difficult to discern between structural, cellular, and molecular changes that uniformly occur in LVAD patients regardless of possible myocardial recovery and changes that occur exclusively in patients with LVAD-induced myocardial functional recovery. Therefore, large-scale, translational studies comprehensively evaluating and correlating functional and clinical outcomes with cellular, structural, molecular, and other biological outcomes are urgently needed to identify the clinical and biological signatures of LVAD-induced myocardial recovery that will further improve our prognostic capacity and allow for the identification of new therapeutic strategies to augment myocardial recovery and regeneration.

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Management of Tricuspid Regurgitation by Caval Valve Implantation

From Technical Feasibility to Evaluation of Efficacy

We congratulate Laule et al. (1) for the first reported use of the 29-mm Edwards Sapien XT balloon-expandable valve (Edwards Lifesciences, Irvine, California) for transcatheter venous implantation to treat tricuspid regurgitation (TR). However, when we first investigated and clinically applied the concept of caval valve implantation (CAVI) as a management option for severe TR, we observed major hemodynamic and anatomic limitations that should be considered when selecting patients for this approach (2–6). First, CAVI does not address TR itself but the regurgitation of blood into the caval veins. Because this condition is present only in a subgroup of patients with severe, often long-standing TR and right ventricular (RV) enlargement, hemodynamic proof of caval regurgitation is essential before valve implantation. Second, CAVI increases RV afterload by exclusion of backward regurgitation. Thus, this novel approach should be reserved for patients with preserved RV systolic function and without elevated pulmonary vascular resistance. In the aforementioned patient group, there is considerable variation in the anatomic diameter of the inferior vena cava (IVC), which may reach up to 45 mm. The diameter of the IVC usually exceeds the suitable range for implantation of current, commercially available devices. Therefore, these patients require specifically designed, potentially individualized devices, which are currently not commercially available. In the series presented by Laule et al, the IVC diameter was within the range to allow implantation of 29-mm balloon-expandable devices, which—from our experience—contradicts "hemodynamically" severe TR.

Further issues in the article by Laule et al. (1) deserve clarification. First, the clinical benefit observed in these patients, particularly the reduction of edema and ascites, is frequently affected by the improved medical therapy and close clinical follow-up they are given. In the data presented, there is no obvious change in echocardiographic parameters to substantiate clinical improvement. Improved RV function as stated in the text is not supported by the data presented and is unlikely for the aforementioned reasons. Lack of documentation of pressure-derived parameters such as RV end-diastolic pressure and mean right atrial pressure further complicates the justification of procedure-related clinical improvement. Second, the authors unfortunately did not present imaging studies or invasive hemodynamic data demonstrating function of both valves. Considering the overall status of the patients, we consider this information essential to actually support the hemodynamic and clinical benefit in these patients.