Adaptations to Pulsatile Versus Nonpulsatile Ventricular Assist Device Support

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The refinement of mechanical cardiac assist devices over the past 50 years largely has been driven by the clinical imperatives to provide reliable circulatory support to patients waiting for cardiac allografts (bridge to transplant) or long-term support for patients with very advanced heart failure (destination therapy). In the course of increasing success with these applications, investigators from numerous centers also have demonstrated that circulatory support with a ventricular assist device (VAD) provides a unique window into the plasticity of the failing human heart. Indeed, since Levin et al first described reverse remodeling of VAD-supported hearts in 1995, there have been scores of original publications documenting the rather striking impact of VAD support on the phenotype of the failing heart. As highlighted in several recent reviews, VAD support promotes regression of pathological cardiac hypertrophy at the organ, tissue, and cellular level, including improvements in many of the signature pathological abnormalities characteristic of failing human hearts.

Article see p 546

The remarkable degree of tissue-level plasticity demonstrated by VAD-supported hearts has furthered the concept that favorable myocardial adaptations may sometimes be sufficient to permit weaning from VAD support with sustained clinical improvement in the syndrome of heart failure (bridge to recovery). However, efforts to achieve sustained myocardial recovery enabling weaning from VAD support have met with variable and often disappointing results. Excluding patients with acute myocardial dysfunction due to aborted ischemic events (stunning), acute myocarditis, or peri-partum cardiomyopathy, reported rates of recovery have varied between 7% and 55%, with most series reporting that <20% of patients can be successfully weaned from VAD support. Besides evidence that reverse-remodeled hearts remain abnormal, both patient selection and a lack of validated management strategies likely contribute to low rates of sustained weaning. With respect to patient selection, the fact that VADs typically are deployed late in the course of heart failure, when some hearts may be unsalvageable, likely biases results toward unsuccessful weaning from VAD support. Likewise, the lack of validated recovery biomarkers exacerbates uncertainty about ideal timing for weaning from VAD support, and incomplete development of potentially beneficial adjuvant therapies are additional contributors to low rates of successful VAD weaning. In this regard, it is relevant that the highest rate of durable weaning from VAD support was achieved in a protocol that included minimally invasive device removal, protocol-driven pharmacological therapy, careful attention of nutrition and extracardiac fitness, and repeated testing to define the degree of functional recovery.

Although the large expense of developing and manufacturing VADs largely has precluded the preclinical animal studies of VAD-induced recovery, some mechanistic insights have been derived from clinical application of VAD support. For example, the concept that myocardial unloading is the most important factor driving structural and functional reverse remodeling during VAD support is supported by observations of greater regression of cellular hypertrophy and improvements in contractile reserve in the unloaded left ventricular (LV) myocardium compared with the less-unloaded right ventricular myocardium. By relating the duration of VAD support to the extent of myocardial remodeling, other studies indicated that different facets of the reverse remodeling proceed at different rates, with reductions in myocyte size proceeding relatively quickly compared with more gradual remodeling of the extracellular matrix during VAD support. Finally, functional comparisons with normal human myocardium obtained from organ donors and broad profiles of myocardial gene expression have clearly shown that hearts substantially improved after VAD support remain quite distinct from normal hearts.

In this issue of Circulation: Heart Failure, Kato and colleagues present results of another effort to exploit variations in the clinical application of VAD support that might provide new insights into the biology of myocardial plasticity. The authors recognize that much of the literature demonstrating VAD-associated reverse remodeling at the tissue level was generated during the era when pulsatile-flow (PF) VADs were the dominant support platform but that most VADs currently implanted are continuous-flow (CF) devices. Accordingly, the aim of their study was to compare 31 PF-supported patients and 30 CF-supported patients based on echocardiographic parameters, circulating biomarkers, and myocardial histology and gene expression. Echocardiograms including tissue Doppler parameters were obtained from all patients within 5 days before the LVAD surgery and at 1 month after the surgery. Plasma brain natriuretic peptide (BNP) was measured within 5 days before the LVAD surgery.
and at various time points after the surgery. Myocardial specimens were collected at the time of LVAD implantation and explantation in a subset of patients (n=21). Although most of the PF-supported patients were enrolled before the CF-supported patients, the groups were well-matched based on markers of heart failure severity, duration of disease, time on VAD support, demographics, and medical therapy. For the CF-supported cases, 27 of 30 were supported with the HeartMate II device.

Although all baseline data were equivalent in the 2 groups, greater reductions in LV end-systolic dimension, E/E', and circulating BNP levels suggest that the magnitude of LV unloading induced by PF VADs was greater than that induced by CF VADs. Furthermore, an increase in LV ejection fraction (EF), fractional shortening, and positive dP/dt in the PF VAD group compared with no change in LVEF and a significantly smaller increment in dP/dt in the CF VAD group also suggests that PF VADs achieved a greater degree of LV mechanical unloading. In addition to the greater reductions in circulating BNP, patients supported with PF VADs also manifested greater reductions in several circulating levels of biomarkers associated with extracellular matrix remodeling, including MMP (matrix metalloproteinase) 9, TIMP (metalloproteinase inhibitor) 4, and osteopontin. Interestingly, despite the apparent differences in the degree of increased myocardial function between patients with PF-supported VAD and patients with CF-supported VAD, both groups demonstrated striking and virtually identical decreases in myocardial expression of BNP, extracellular matrix-regulating genes, levels of myocardial fibrosis, and the average reduction in cardiac myocyte cross-sectional area.

As a composite, the findings raise several interesting questions about the assessment of myocardial reverse remodeling and the relative merits of PF versus CF devices. For example, do the apparently lesser improvements in LVEF and positive dP/dt observed with CF VAD support represent lesser improvements in intrinsic contractile performance and intracellular calcium cycling dynamics, or is it just a reflection of reduced cyclic elastic recoil that is expected with CF VADs? The fact that the pulsatility index parameter, reflecting myocardial contribution to VAD flow, tends to acutely decrease with higher VAD speeds (inducing greater chamber decompression), indicates that LV pump dynamics are preload dependent in the setting of CF VADs. From this perspective, the association of a lesser degree of unloading with a lesser improvement in LVEF and dP/dt seems paradoxical. On the other hand, the finding of lesser improvements in LVEF and dP/dt might be consistent with the concept that unloading is the primary stimulus for improved contractility after VAD support. Another alternative is that metrics like LVEF and dP/dt must be interpreted differently in the setting of different types of VAD support such that the greater preservation of cyclic elastic recoil with the PF VADs tends to produce greater increases in these metrics independent of intrinsic myocardial contractility. This difficulty in assessment of LV systolic and diastolic function between these 2 distinct VAD platforms highlights the need for a load-independent index of myocardial function. If the echocardiographic measures of systolic and diastolic function had been captured at the time of an LVAD pump on/off study (in the case of a PF device) or an LVAD turn-down study (in the case of a CF device), a greater degree of confidence in the differential improvement of myocardial function with PF than with CF support would be present. Ultimately, this speculation would best be examined with direct in vitro comparisons using isolated muscle strips and/or isolated myocytes to extend the initial studies demonstrating functional reverse remodeling in VAD-supported patients.

The findings by Kato et al also raise questions about the type and degree of unloading that is required to induce substantial morphological and molecular reverse remodeling. The fact that equivalent reductions in cardiac myocyte cross-sectional area and the abundance of several myocardial genes occurred with apparently lesser degrees of myocardial unloading in the CF groups could suggest a nonlinear stimulus-response relationship for these parameters. Alternatively, qualitative differences in unloading may have a significant impact on the myocardial adaptations independent of the absolute degree of unloading. In PF VAD support, the lack of synchrony between VAD and native cardiac cycle dynamics produces greater variability in intraventricular systolic pressures than are observed with CF VAD devices. These periodic differences, with intermittent native LV contraction against a closed LVAD inflow valve in PF VADs, may offset the overall greater degree of diastolic unloading produced by PF VADs, resulting in equivalent reductions in fibrosis, myocyte size, and associated changes in the expression of matrix-regulating genes in patients supported by PF or CF VADs. From this perspective, the equivalent changes in myocyte cross-sectional area and gene expression observed with CF and PF VADs suggest that the net, time-averaged unloading at the tissue level is actually equivalent in the 2 groups.

The fact that intergroup differences in the circulating biomarkers (BNP, MMP9, TIMP4, and osteopontin) were not paralleled by intergroup differences in the expression of the same genes within the LV myocardium raises doubts about the ability of these biomarkers to reflect the molecular dynamics within the supported ventricles. Although the authors highlight several factors that could explain the discordance observed (extracardiac effects, contributions of chambers that are not as dramatically unloaded, etc), the fact remains that the need for easily measured biomarkers reflecting meaningful myocardial recovery has not yet been met.

Although the current studies do not permit definitive conclusions regarding whether the CF VADs that are now most frequently used will be equivalent or superior to PF VADs for permitting weaning from VAD support, the results presented inspire several important considerations while moving forward. If there is a difference in the improvement in LV function with PF versus CF support, is this because of increased mechanical unloading? The data presented here do not support this mechanism at all because there was no significant difference in the change in LV end-diastolic diameter, myocyte cross-sectional area, or myocardial gene expression of BNP, MMP2, MMP9, TIMP1, TIMP4, and osteopontin. This may be the most important finding in the study by Kato et al because it calls for an alternative
mechanism to explain the difference in LV systolic and diastolic function. An alternative consideration is the physiological consequence on the peripheral vasculature of long-term mechanical support with CF pumps. Although few patients are fully nonpulsatile, the majority of patients on CF VAD support demonstrate an increase in diastolic blood pressure resulting in a markedly decreased pulse pressure. Future studies investigating differences in systemic endothelial dysfunction, neurohormonal deactivation, and renal function (all known to affect LV systolic and diastolic function) may provide another component to consider in designing the optimum platform of mechanical support to achieve the most robust degree of myocardial recovery with VAD support.

Disclosures

None.

References


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