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EDITORIAL COMMENT

Echocardiographic Identification of Elevated Filling Pressures in LVAD Patients*

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If you don't know where you are going,
you might wind up someplace else.

Yogi Berra (1)

Mechanical circulatory support systems, such as continuous-flow left ventricular assist devices (CF-LVADs), are being increasingly used as destination therapy or bridge to heart transplantation in patients with end-stage heart failure. The rate of implantation has nearly doubled since 2010, with >5,000 devices placed in the last 2 years in the United States alone (2). Despite survival improvement with these devices, the clinical course of the patient is punctuated by a number of adverse events, including residual heart failure, which frequently warrants additional investigations.

Inadequate left ventricular (LV) unloading, often as a consequence of suboptimal left ventricular assist device (LVAD) parameters or comorbidities, is central to the worsening symptoms; some of these events can be treated with simple but effective options (e.g., optimize the device settings, use diuretics). However, other causes, such as right ventricular (RV) failure, can present with heart failure–like symptoms (edema, elevated jugular venous pressure, and shortness of breath on exercise), in which such treatment may be less effective and, in certain situations, even harmful. An accurate estimate of LV filling pressures, a good surrogate of LV unloading, would be invaluable in this scenario. Current guidelines support the use of right heart catheterization (RHC) (3) to aid clinical management in such settings to optimize LVAD parameters in these patients. However, invasive hemodynamic assessment is uncomfortable and carries a small but definite procedural risk in anticoagulated patients. Although definite data are lacking, it is estimated that thousands of RHCs are performed each year in the LVAD population, with some patients needing many such procedures over their lifetime. The ability to gauge filling pressures noninvasively would therefore be of great advantage.

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In this issue of the *Journal*, Estep et al. (4) validate, for the first time, the reliability of echocardiography in estimating LV filling pressures obtained through catheterization in 50 prospectively enrolled patients with CF-LVADs (40 in the derivation cohort and 10 in the validation cohort) who underwent clinically indicated RHC. Multiple echocardiographic indices were compared with simultaneous invasive RHC measurements. There were 2 major findings. First, noninvasive measurements of pressures (right atrial [RA] and pulmonary artery) correlated well with invasive ones, which has been shown before but in smaller studies. RV stroke volume and pulmonary vascular resistance, however, showed only modest correlation. Second, the authors devised an echo algorithm combining the E/A ratio (ratio of mitral valve peak early [E] and late [A] diastolic velocities) with 3 other echocardiographic parameters and found a 90% accuracy in differentiating between "high" versus "not high" LV filling pressures. This is a good first step to a complex, fairly common problem. This algorithm, if validated elsewhere, will be useful in clinical practice if it can avoid RHC in some patients.

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Unfortunately, although left atrial (LA) pressure is a strong predictor of symptoms, and a major prognostic factor for outcome (5), very limited data are available on how well one can noninvasively assess LA pressures in LVAD patients. A number of echo parameters currently are being used to gauge the adequacy of filling pressures and LV unloading in CF-LVAD patients. Although intuitively useful, many of these have not been rigorously validated at the current time. Given the controversy regarding the use of the E/e' ratio (mitral inflow early diastolic filling peak velocity/early diastolic mitral annular velocity) in defining LA pressure in patients with advanced heart failure (6,7), we need to thoroughly validate noninvasive measures of LA pressure in the setting of a CF-LVADs. A comprehensive method to identify and quantitate LA pressure under different pathophysiological conditions might be critical.

Currently, RHC is the primary method to estimate RA and LA pressures in CF-LVAD patients presenting with symptoms of suboptimal LV unloading (class IB). Given the importance of accurate assessment of pulmonary vascular resistance, there will continue to be a role for invasive hemodynamic evaluation in CF-LVAD patients, particularly those who are candidates for heart transplantation (3). Physical examination is a disappearing skill, and there are few objective data to show that it accurately predicts LA pressure in most patients supported with an LVAD. Noninvasive methods are attractive, and some echo parameters may be useful, but the severe paucity of data in this space is reflected in the fact that 2 recent major reviews addressing the role of echocardiography in LVAD patients did not mention any strong studies supporting noninvasive prediction of LA pressure (8,9). The few available studies with any validation using invasive hemodynamic measurements have been very small (<10 to 15 patients), were often a small part of another study, and mainly limited to correlative conclusions rather than providing absolute cutoff values.

Do we need to estimate LA pressure itself or can another surrogate substitute for it in decision making? Some studies have incorporated serial changes between RV and LV end-diastolic sizes post-LVAD and on follow-up, in evaluating for optimal unloading and thereby indirectly assess filling pressures. LV diastolic size decreases post-LVAD implantation due to decompression, but chronic support can be associated with an increase in LV size even while not adversely affecting symptoms (10). Nevertheless, ramp studies have used LV size as one useful endpoint to optimize LV unloading (11). Interestingly, this ramp protocol did not use any direct measure of LV filling pressures. Others have used septal position in decision-making strategies for optimally unloading of the left ventricle. However, the relation between chamber pressures is complicated. LVAD consistently unloads the left ventricle with a reduction in LA pressure but has variable effects on RA pressure that can remain unchanged, decrease (if severe pulmonary arterial hypertension and RV failure is improved), or even increase from better venous return (12). Similarly, interventricular septum shifts while representing LV unloading might also be influenced by RV dysfunction and tricuspid regurgitation, further complicating its ability to predict therapeutic changes (9). Topilsky et al. (5) showed reasonable correlation ($r = 0.74$) between echo estimates of LA pressure (on the basis of position of interatrial septal position) and RHC-measured wedge pressure in 8 subjects. This finding was replicated in the study by Estep et al. (4) but was not found to be useful to incorporate in the algorithm. Finally, the pattern of LV filling has been used with modest correlation to filling pressures in some studies. These features did not seem to add to predicting LA pressure with good specificity in the present study. The role of brain natriuretic peptide (BNP) in predicting LA pressure has been inadequately studied in LVAD patients. Paradoxically, higher BNP levels predicted fewer readmissions in 1 large study (13), and BNP levels correlate only modestly with wedge pressures in CF-LVAD patients (14). We therefore have few direct measures of LA pressure in CF-LVAD patients, and the index presented in the present study by Estep et al. (4) is a good start.

The strengths of the study by Estep et al. (4) are obvious: the importance of the problem they address; the number of patients from a single center studied prospectively with comprehensive simultaneous echo and RHC measurements; and a validation cohort, albeit small. The authors also showed that although individual echo components may correlate well with elevated pulmonary capillary wedge pressure, none of them is clinically useful by themselves, lacking good positive and negative predictive values. The E/e' ratio, a good marker of filling pressure in patients with heart failure, did not differ very significantly between CF-LVAD patients with and without high LA pressure. A composite of multiple variables seemed to provide the best estimate.

The limitations of this study (4) are the highly selected patient population with mainly normal or only mildly reduced RV systolic function. Applicability may be limited in patients with atrial fibrillation, RV failure, and/or previous mitral valve

surgeries. In the group that was short of breath, one could argue that dyspnea alone would have predicted a high filling pressure in a large proportion of them. The algorithm identified elevated wedge pressures with reasonable accuracy (~90%), but the index was feasible in only three-fourths of the population. Future real-world studies involving multiple centers should address this issue. The algorithm also needs to be validated in other devices (e.g., HeartWare HVAD [HeartWare Inc., Framingham, Massachusetts) and other pump speeds.

It is gratifying that, within the aforementioned limitations, we can noninvasively estimate LV filling pressures with decent accuracy in patients with CF-LVADs. A subset of CF-LVAD patients who will benefit from this echocardiographic assessment may be spared from an invasive RHC. The next step should be to demonstrate that this echocardiographic index is actionable and sensitive to changes in filling pressures. Finally, it remains to be seen whether making clinical decisions on the basis of "echo data" alone can improve outcomes without needing RHC in patients with residual heart failure. This would greatly increase the utility of this algorithm. In the end, the goal is to produce better strategies for improving patient symptoms and longevity by optimally unloading the heart, while minimizing risks from unnecessary diagnostic testing.

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