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EDITORIAL COMMENT

Dealing With Unintended Consequences

Continuous-Flow LVADs and Aortic Insufficiency*

James C. Fang, MD, Omar Wever-Pinzon, MD

Over the last decade, left ventricular assist devices (LVADs) have assumed an increasingly important role in the management of patients with advanced heart failure (1). There are now more than 20,000 implants worldwide, and support times have even exceeded 10 years in individual cases. In transplant-ineligible patients, LVADs have dramatically improved survival and now provide a practical therapeutic option for these patients; destination therapy (or "permanent" implantation) now represents 42% of the total implants in the United States (1). In addition, there is growing interest in the use of LVADs to facilitate myocardial recovery such that device explantation can now be considered (2).

Mechanical circulatory support, however, produces marked alterations in normal physiology, leading to unanticipated adverse effects, particularly in nonpulsatile, continuous-flow (cf) LVADs. Aortic insufficiency (AI) is one of those unforeseen complications. Approximately one-third of patients will develop at least mild to moderate AI (using traditional methods of assessing AI) after a median of 6 months (3). The etiology of cf-LVAD-associated AI is due to several factors (**Figure 1**), including reduced valve opening, altered blood flow dynamics, pancyclic transvalvular gradients, high shear stress, and leaflet malcoaptation. These processes promote leaflet fusion, valve degeneration, and aortic wall remodeling, which ultimately lead to AI (4,5). These functional and anatomic changes take their toll over time; 15% of patients will eventually experience moderate to severe AI (5), which can limit the "durability" of LVAD therapy.

Eventually, the regurgitant volume prevents adequate LV unloading, and LV end-diastolic pressure will rise. In addition, forward cardiac output is compromised by an endless loop situation in which blood circulates through the LVAD into the ascending aorta but then back into the LV through the incompetent aortic valve, then back through the LVAD, and so on. If the regurgitant volume is great enough, heart failure symptoms develop. At that point, LVAD speed modulation or aortic valve interventions are considered; urgent transplantation may even be entertained (5).

Accurate assessment of AI, however, is a challenge, even in the non-LVAD-supported patient. The lack of a true gold standard technique for comparison amplifies this difficulty. Invasive measures of regurgitant fraction or volume rely on complex calculations and assumptions that may not hold true in cf-LVAD patients, in whom native circulation has been altered to provide continuous flow between the ventricular apex and the ascending aorta, while simultaneously the native heart function is providing intermittent pulsatile flow through the aortic valve into the aortic root. As one can imagine, uncertainty exists about the most appropriate diagnostic approach to assess AI in such a disrupted circulation.

The American Society of Echocardiography (ASE) has defined guidelines for measuring and categorizing AI severity. However, these definitions are likely not applicable during cf-LVAD support because continuous unloading generates a reverse transvalvular gradient that reduces aortic valve opening and results in continuous (systolic and diastolic) AI if the valve is incompetent. The magnitude of the reverse transvalvular gradient and degree of AI in the cardiac cycle will depend on LVAD speed, LV contractility, and loading conditions. Consequently, such issues make previous reports of AI in cf-LVADs, which have used traditional ASE criteria, difficult to interpret.

In this issue of *iJACC*, Grinstein et al. (6) provide an elegant evaluation of traditional and novel

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From the Division of Cardiovascular Medicine, University of Utah Health Sciences Center, Salt Lake City, Utah. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

parameters to assess AI severity in cf-LVAD patients and, importantly, also correlate it with LV filling pressures as a measure of heart failure. Twenty patients with different degrees of AI (7 patients without AI) were prospectively enrolled and underwent simultaneous right heart catheterization and echocardiographic evaluation. Two traditional echocardiographic measures of AI, the vena contracta and visual estimation, were compared with 2 novel echocardiographic parameters, LVAD outflow cannula diastolic acceleration and LVAD outflow

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cannula systolic-to-diastolic velocity ratio. The regurgitant fraction was cleverly obtained by subtracting the right-sided cardiac output obtained at catheterization from the total left-sided flow, summed from the LVAD cannula outflow and aortic valve flow (obtained from echocardiography). Imaging of the LVAD outflow cannula to measure LVAD flow was feasible in most but not all patients. These parameters were correlated with each other and with the invasively determined pulmonary capillary wedge pressure (PCWP). The performance of the novel parameters was also evaluated under different loading conditions in 5 patients with the use of a ramp protocol.

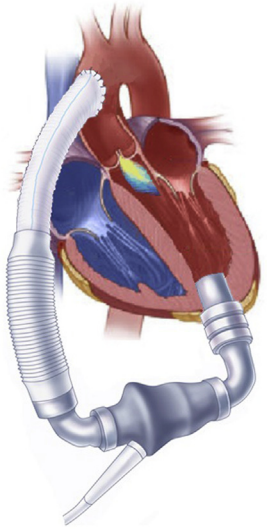
A number of relevant observations were made: 1) the vena contracta method underestimated and poorly correlated with the PCWP; 2) the LVAD outflow cannula systolic-to-diastolic velocity ratio provided the best correlation with LV filling pressures at rest and under different loading conditions (i.e., ramp test); 3) the regurgitant fraction was strongly correlated with LV filling pressures; and 4) the LVAD outflow cannula diastolic acceleration had a modest correlation with LV filling pressures.

What are the implications of these findings? First, these data substantiated that traditional echocardiographic parameters to assess AI severity do not reflect meaningful hemodynamic consequences and should be reconsidered for use in clinical practice. Of note, the visual estimation method did seem to correlate well with the regurgitant fraction, but correlation with PCWP was unclear. Second, the strong correlation of LVAD outflow cannula systolic-to-diastolic velocity ratio and the regurgitant fraction with the PCWP suggests that these measures could be used to assess AI severity in cf-LVAD patients, although thresholds for concern remain to be determined.

There are limitations to this work that need to be considered. First, although carefully conducted and prospective, the study involved 20 patients, of whom only 13 had AI. Moreover, regurgitant fraction could not be determined for all of the patients (i.e., 75%). Second, the exclusive enrollment of HeartMate II LVAD patients limit the extrapolation of these data to patients supported by different devices. In particular, centrifugal LVADs are more sensitive to changes in afterload because they operate on a flat H/Q curve (pressure head vs. flow) and provide greater LV unloading during systole in contrast to the greater unloading during diastole with axial flow pumps. Moreover, centrifugal pumps demonstrate different flow mechanics when the aortic valve is in closed versus open position, compared with the axial flow of the HeartMate II (7). Third, the determination of regurgitant fraction also required an invasive procedure for the estimation of cardiac output by the assumed Fick method, which on its own has limitations. Ideally, all of the information required for the estimation of the regurgitant fraction would be obtainable by echocardiography. Validation of noninvasively derived forward cardiac output in cf-LVAD patients will be required in future studies.

The noninvasiveness and strong correlation between the PCWP and the LVAD outflow cannula systolic-to-diastolic velocity ratio make this parameter attractive to incorporate into routine clinical practice. However, further experience is needed to

FIGURE 1 Mechanisms Responsible for the Development of AI in Patients on cf-LVAD Support



Abnormalities in Flow Dynamics Induced by cf-LVADs

1. Reduced AV opening
2. Local stasis
3. Reversed transvalvular PG (high)
4. Pan-cyclic transvalvular PG
5. High shear stress

Histopathological Changes Leading to AI in cf-LVADs

1. Increased local fibrosis and thrombus formation
2. Aortic root remodeling and dilatation
3. AV degeneration and remodeling
4. AV commissural fusion
5. AV leaflets malcoaptation

AI = aortic insufficiency; AV = aortic valve; cf-LVAD = continuous-flow left ventricular assist device; PG = pressure gradient.

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determine the effects of outflow cannula-related (e.g., positioning and kinking) and patient-related factors (e.g., heart rate, systemic vascular resistance, aortic root size, changes in contractility) on this measurement. Patients in this cohort were also relatively young (in their 50s), and it is uncertain how aging and vascular remodeling, not uncommon in destination therapy patients, could affect the performance of these parameters. In addition, the routine ability of varied sonographers to obtain these echocardiographic windows and flows remains unclear. Lastly, the goal of any diagnostic test is to impact clinical decisions and patient management; thus, correlation of these novel AI parameters with symptoms, clinical presentation, and/or mortality will need further elucidation.

In summary, this study established that traditional measures of AI are inadequate and new measures (LVAD outflow cannula systolic-to-diastolic velocity ratio and regurgitant fraction) better reflect the degree of AI and its consequences. However, this study may ultimately be a reminder that perhaps human circulation was not meant to be continuous; unintended consequences should not be a surprise when an evolutionarily designed pulsatile system is asked to become continuous.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. James C. Fang, University of Utah Health Sciences Center, Division of Cardiovascular Medicine, 30 N. Medical Drive, 4A100 SOM, Salt Lake City, Utah 84132. E-mail: james.fang@hsc.utah.edu.

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KEY WORDS aortic insufficiency, heart failure, LVAD