EDITORIAL COMMENT

Factors Influencing the Rate of Flow Through Continuous-Flow Left Ventricular Assist Devices at Rest and With Exercise*

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The heart failure (HF) community has witnessed a rapid evolution in mechanical circulatory support over the past decade. Following publication of the pivotal HeartMate II trials, continuous-flow left ventricular assist devices (cLVADs) with an axial rotor (e.g., HeartMate II) quickly replaced the first-generation, pulsatile devices as both a bridge to transplant and as destination therapy for patients with advanced HF (1,2). The centrifugal-flow LVADs (e.g., HeartWare) have recently been approved as a bridge to transplant and are another alternative for patients with advanced HF (3). Major advancements with these newer cLVADs include a smaller design and long-term durability compared with the larger, pulsatile LVADs (4). However, questions remain over the effects of long-term exposure to nonpulsatile or minimally pulsatile flow on the human body. Moreover, it is uncertain how these devices respond to changes in loading conditions that occur during exercise to match perfusion with metabolic demand.

The cLVAD consists of inlet and outlet cannulae, as well as a rotor, which is responsible for propelling blood throughout the body (5). Currently, the rotor is set at a fixed pump speed for optimal unloading of the LV. Although pump speed is the primary determinant of pump flow rate (independent of any regulatory signals from the body), changes in the head pressure, or differential pressure across the pump (aortic pressure minus ventricular pressure) brought on by changes in pre-load and/or afterload, influence overall pump output (5,6). As the head pressure increases, flow through the LVAD decreases (5,7). This physiology underscores the importance of blood pressure control because elevated arterial pressures increase the head pressure, leading to greater impedance of flow and a reduction in pump output (8). In a similar fashion, a reduction in pre-load translates into a wider pressure differential across the pump, which in turn leads to reductions in flow through the device (5).

In this context, there is great interest in further examining the effect of changes in loading conditions, such as those that occur during exercise, on LVAD flow. The ability to augment flow (i.e., cardiac output) during increases in metabolic demand is one of the key factors regulating the cardiovascular response to exercise and, in normal individuals, is remarkably independent of age, sex, or fitness (9–11). The signals to augment cardiac output come primarily from skeletal muscle; when such signals are deranged, cardiac output may increase out of proportion to metabolic demand (12,13). Conversely, patients with severe HF may not be able to augment cardiac output adequately due to impaired myocardial contractility, which is a harbinger of a poor outcome (14).

How cardiac output may be regulated during exercise in patients in whom these metabolic and mechanical afferent signals are divorced from the
ultimate response (blood flow delivery), such as in patients with LVADs, has not been well studied. Moreover, the importance of nonpulsatile flow, which greatly alters baroreflex function at rest (15), has rarely been considered during exercise. Several previous analyses have demonstrated that flow increases during aerobic exercise in LVAD patients with a treadmill (16) and cycle ergometry (17-20). In this issue of \textit{JACC: Heart Failure}, Muthiah et al. (21) hypothesized that the mechanism by which increased LVAD flow occurs is likely related to either an increase in venous return or intrinsic heart rate (HR) and sought to determine the relative extent to which these 2 factors influenced LVAD flow.

To accomplish these objectives, 11 patients with HeartWare centrifugal-flow LVADs and pacemakers were enrolled in 2 separate studies. First, HR was changed by either increasing (approximately 40 beats/min) or decreasing (approximately 30 beats/min) the pacemaker rate. Despite these large changes in intrinsic HR, LVAD flow was minimally affected (baseline flow rate 5.21 ± 1.3 l/min; flow rate at maximum HR 5.17 ± 1.2 l/min; \( p = 1.0 \)). Such an outcome would be expected if there was little contribution of the intrinsic LV to forward cardiac output, although it is possible that increasing HR could improve right-sided cardiac output and thereby improve LVAD filling.

In a second study, the effect of pre-load on pump flow was assessed in 10 patients by a tilt-table assessment at supine, 30°, 60°, and 80° head-up tilt (HUT). The change in body position from supine to 30° led to a reduction in flow (baseline flow 4.9 ± 0.6 l/min; flow at 30° HUT 4.5 ± 0.5 l/min; \( p < 0.01 \)), but no further reductions were observed at 60° or 80° HUT. After 3 min in each position, patients were asked to perform active ankle flexion exercises to increase venous return to the heart, which increased flow back to the baseline value. It is important to emphasize 2 things about this protocol. First is that the head-to-foot gravitational gradient (Gz) is proportional to the sine of the tilt angle. Therefore 50% of this gradient is achieved at an angle of 30°, 87% at 60°, and 98% at 80°; therefore, there is about half as much blood pooling below the heart at 30° compared with 80°. The degree to which right ventricular (RV) stroke volume is affected depends on the Starling curve of the RV, RV compliance, venous compliance, and the presence of pericardial restraint; thus, the reader should be cautious before assuming that the majority of venous pooling occurs at 30° upright tilt as stated by the authors. The fact that 20° head-down tilt had minimal effect on flow through the LVAD suggests that RV and consequent LV filling were already maximized in the supine position and is not surprising. Second, because of the increased Gz gradient with increasing tilt angle, the patients had to lift twice as much weight during toe raises at the higher compared with the lower tilt angles. Although the muscle pump is maximally activated at lower contraction intensities, the stimulation of both metabolic and mechanical afferents is increased with the intensity of muscle contraction (22). That is the likely explanation for why blood pressure was elevated by nearly 10 mm Hg when toe raises were performed at 80° compared with 30°, which may well have influenced the flow outcomes.

Although these results do shed some light on the mechanism by which exercise increases the LVAD flow rate (Fig. 1), there are several considerations and potential confounders that must be addressed. First, pacing-induced increases in HR under resting conditions may not elicit the same physiological response as exercise-induced increases in HR. In healthy individuals, increases in cardiac output with exercise result from a reduction in peripheral resistance, along with increases in contractility, venous return (thereby increasing stroke volume), and HR. Recent studies in healthy individuals failed to show a relationship between pacing-induced increases in HR and augmentation of cardiac output during exercise (23,24). Almost a century ago, Bainbridge (25) described exercise-induced increases in HR as a response to increased venous return, stating that
“when venous filling is increased, the circulation can be maintained by the more rapid transference of blood from the venous to the arterial system.” Thus, the lack of a relationship between increases in paced HR and LVAD flow under resting conditions in the study by Muthiah et al. (21) did not sufficiently replicate the physiological response to exercise.

Second, the potential role for other aforementioned responses to exercise (i.e., reduced peripheral resistance and increased contractility) on LVAD flow was not fully explored in the current study. Specifically, neither stable ventricular dimensions nor unchanged frequency of aortic valve opening are adequate surrogates for more subtle changes in contractility. Increased contractility of either the RV, by delivering more blood to the LV, or the LV, by propelling blood faster through the LVAD, could theoretically increase LVAD flow. We recognize that in HF, exercise-related increases in contractility are less pronounced than those in healthy individuals; however, it may be that contractile reserve improves following months of unloading by an LVAD (16). As an example, Jakovljevic et al. (16) showed that stroke volume during exercise was greater in patients with cfLVADs than those with advanced HF without LVADs.

RV function can have a major impact on LVAD flow rate (26) because a severely dysfunctional RV may not be able to adequately fill the LV, which would limit increases in flow during exercise. In the current study, 6 of the 11 patients evaluated had imaging evidence of RV systolic dysfunction and there were no differences between those with preserved or impaired RV function when the impact of changes in HR on the LVAD flow rate were examined. However, given that the severity of RV dysfunction in the study by Muthiah et al. (21) was not provided (RV dysfunction was defined as mild dysfunction or greater) and the small sample size of patients evaluated, it is difficult to draw any firm conclusions on the contribution of the RV, or lack thereof, to exercise-induced increases in flow.

Finally, it is worth mentioning that this study evaluated patients with centrifugal-flow HeartWare LVADs. Differences in intrinsic properties of axial and centrifugal-flow pumps lead to profound differences in response to changes in head pressure (8). An analysis of the pressure-flow curve of these devices reveals that the centrifugal-flow LVADs are more sensitive to changes in head pressure than axial-flow devices. This results in greater changes in flow for any given change in pressure across the pump. In this regard, conclusions from this study should not be generalized to patients with axial-flow devices without first acknowledging the fundamental differences in flow characteristics between the different devices. A follow-up study comparing the response of axial-flow and centrifugal-flow LVADs to exercise would be of great interest.

Muthiah et al. (21) are to be congratulated for advancing the field. Their study has effectively demonstrated that hydrostatic gradients induced by position changes under resting conditions influence LVAD flow rate. This is likely one mechanism by which exercise leads to increases in pump flow rate, by augmenting venous return to the RV via the muscle pump. Secondly, they convincingly demonstrated that manipulations of intrinsic HR under resting conditions had no significant impact on LVAD flow rate in this study, with the caveat that a pacing model does not fully mimic the effect of increased HR (through vagal withdrawal and sympathetic activation) during exercise in patients with cfLVADs. This study sets the stage for additional investigation into other potential factors that increase cfLVAD flow under exercise, with the most obvious being contractile reserve of either or both ventricles.

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KEY WORDS exercise, heart rate, LVAD, posture, tilt-table