Original Article

Blood Pressure and Adverse Events During Continuous Flow Left Ventricular Assist Device Support

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Background—Adverse events (AEs), such as intracranial hemorrhage, thromboembolic event, and progressive aortic insufficiency, create substantial morbidity and mortality during continuous flow left ventricular assist device support yet their relation to blood pressure control is underexplored.

Methods and Results—A multicenter retrospective review of patients supported for at least 30 days and ≤18 months by a continuous flow left ventricular assist device from June 2006 to December 2013 was conducted. All outpatient Doppler blood pressure (DOPBP) recordings were averaged up to the time of intracranial hemorrhage, thromboembolic event, or progressive aortic insufficiency. DOPBP was analyzed as a categorical variable grouped as high (>90 mm Hg; n=40), intermediate (80–90 mm Hg; n=52), and controlled (<80 mm Hg; n=31). Cumulative survival free from an AE was calculated using Kaplan–Meier curves and Cox hazard ratios were derived. In the high DOPBP group only 1 (3%) in the controlled DOPBP group and only 1 (3%) in the intermediate DOPBP group. The likelihood of an AE increased in patients with a high DOPBP (adjusted hazard ratios [95% confidence interval], 16.4 [1.8–147.3]; P=0.012 versus controlled and 2.6 [0.93–7.4]; P=0.068 versus intermediate). Overall, a similar association was noted for the risk of intracranial hemorrhage (P=0.015) and progressive aortic insufficiency (P=0.078) but not for thromboembolic event (P=0.638). Patients with an AE had a higher DOPBP (90±10 mm Hg) in comparison with those without an AE (85±10 mm Hg; P=0.05).

Conclusions—In a population at risk, higher DOPBP during continuous flow left ventricular assist device support was significantly associated with a composite of AEs. (Circ Heart Fail. 2015;8:551-556. DOI: 10.1161/CIRCHEARTFAILURE.114.002000.)

Key Words: aortic valve insufficiency ■ blood pressure ■ cerebral hemorrhage ■ thrombosis

Although heart transplantation remains the gold standard treatment for end-stage heart failure, donor shortage has necessitated the development of an alternative cardiac replacement therapy. To address this demand, the field of mechanical circulatory support has grown tremendously over the past 15 years. Because of exorbitant wait times and stringent eligibility criteria for heart transplantation, the number of people, both as bridge to transplantation and destination therapy, living for extended periods on left ventricular assist device (LVAD) support is on the rise. Current best estimates place the total number worldwide living with a LVAD at >7000. As this figure is expected to increase exponentially in the coming years, refinement in long-term management strategies is needed.

The newest generations of LVADs are rotary blood pumps using either centrifugal or axial propulsion. These designs offer significant advantages including pump miniaturization, silent operation, and most importantly, enhanced device durability. Because these pumps move blood from the left ventricle to the aorta throughout the cardiac cycle, they create a nonphysiological continuous blood flow pattern and are referred to as continuous flow (CF) LVADs. With reduced or absent arterial pulse pressure, traditional methods of noninvasive blood pressure measurements are unreliable. This limitation is overcome by using Doppler ultrasound of the brachial artery after an arm cuff is deflated and recording the audible restoration of flow as the Doppler blood pressure (DOPBP). DOPBP has been previously shown to have an excellent correlation to systolic blood pressure measurement via arterial line in CF LVAD subjects.

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Of the most common significant adverse events (AEs) associated with CF LVADs, 3 are potentially modulated by blood pressure. These are (1) intracranial hemorrhage (ICH), (2) thromboembolic events (TEs), and (3) development of severe aortic insufficiency. The recently published International Society of Heart and Lung Transplantation guidelines for Mechanical Circulatory Support acknowledge this potential by recommending that patients with nonpulsatile CF LVADs should have DOPBP goal of ≤80 mm Hg. This recommendation is based on a Level of Evidence C (expert opinion), highlighting the need for an evidence-based rationale of optimal blood pressure targets in this population. Therefore, in the current study, we aimed to examine the association of DOPBP and AEs in patients supported with a CF LVAD.

Methods

Study Population
We retrospectively reviewed all patients undergoing CF LVAD placement from June 1, 2006, to December 31, 2013, at Montefiore Medical Center and Stony Brook University Medical Center. Patients were included if they survived at least 30 days on CF LVAD support and were discharged to the outpatient setting. As per institutional protocols, moderate or greater aortic insufficiency was surgically addressed at the time of LVAD implant and these patient were excluded. The study protocol was approved by the institutional review boards of both centers.

Data Collection
Preoperative clinical information and baseline demographics were collected from medical charts. The analysis commenced at 30 days after implant and after hospital discharge. DOPBP recordings from all outpatient clinical visits were averaged up to the time of the following AE: (1) ICH, (2) TEs, and (3) development of moderate or severe aortic insufficiency, henceforth referred to as progressive aortic insufficiency (pAI). If patients did not have an ICH, TE, or pAI, then DOPBP was averaged until transplantation, device explantation, expiration, or up to 18 months on CF LVAD support. International Normalized Ratio was retrieved at the time of ICH and TE.

Definition of AEs
ICH was defined as the presence of hemorrhage noted on a head computed tomographic scan accompanied by neurological symptoms. TEs included ischemic CVA, peripheral embolism, or device thrombosis. Ischemic CVA was defined as the presence of acute cerebral infarction noted on a head computed tomographic scan accompanied by neurological symptoms. Peripheral embolism was confirmed by radiological imaging. Device thrombosis was defined as the presence of thrombus within the LVAD leading to device malfunction and explantation. All device thromboses were subsequently confirmed by direct inspection and visualization of the pump. Development of pAI was determined by its presence on clinical echocardiograms (based on the American Society of Echocardiography criteria for moderate or severe AI) performed during the course of CF LVAD support.

Data Analysis
Patients were categorized into 3 groups based on their average outpatient DOPBP: (1) high (≥90 mm Hg), (2) intermediate (80–89 mm Hg), and (3) controlled (<80 mm Hg). The primary end point was the occurrence of any AEs. Secondary end points were the occurrence of each individual AE, including ICH, TEs, or pAI. If patients had >1 AE, then analysis of the primary end point was done with the time to the first AE and the time to each individual AE was used in the secondary end point analysis.

Statistical Analysis
Data are displayed as mean±SD. Baseline demographics were compared between patients in all 3 DOPBP groups by ANOVA for continuous variables and the χ2 test for categorical variables. Cumulative survival free from primary and secondary end points was shown using Kaplan–Meier curves, and hazard ratios were calculated by univariable and multivariable Cox proportional analysis. Multivariable analysis was adjusted for variables that may have clinically affected the outcome of interest including age, hypertension, diabetes mellitus, atrial fibrillation, aspirin use, baseline renal function, gastrointestinal bleeding on CF LVAD support, and device type. A value of P<0.05 was considered statistically significant. DOPBP was also compared as a continuous variable between patients with and without the combined end point by the Student t test. Statistical analyses were conducted in SAS version 9.3 (SAS Institute, Cary, NC).

Results

Patient Characteristics
The study group comprised 123 patients who were supported by a CF LVAD for at least 30 days and met the inclusion criteria. Nearly one half (49%) of the total cohort had an ischemic cause of cardiomyopathy and 31% had atrial fibrillation. Table 1 demonstrates the clinical characteristics of these patients and categorized into the 3 DOPBP groups. Patients in the greater DOPBP groups had a higher baseline creatinine (P<0.003) and were more likely to have a history of hypertension (P<0.001). Non-white patients comprised the majority in the high DOPBP group (64%) in contrast to the controlled DOPBP group, which consisted mainly of whites (62%). Aspirin and β-blocker use was high and similar across the groups. Angiotensin-converting enzyme inhibitor and angiotensin receptor blocker use decreased with each successive DOPBP group, whereas the use of the alternative vasodilators hydralazine/nitrate tended to increase (Table 1), perhaps corresponding to differences in the baseline renal function.

On average, there were 10±7 DOPBP readings per patient in the entire cohort during the study period without a significant difference between groups (Table 1). In those patients who had an AE (n=20), the mean number of readings was 6±4. It is important to note that the readings at the time of the event were excluded because BP is known to be artificially elevated especially acutely during a neurological episode.

Prevalence of AE

Twenty (16%) patients in the entire group had a predefined AE during the follow-up period (109 patient years of LVAD support). Eight (6.5%) patients experienced an ICH, 7 (5.7%) had a TE and 6 (4.9%) demonstrated pAI. The median time to first AE was 92 (range, 31–513) days DOPBP. Figure 1 displays the distribution of each type of AE among the 3 DOPBP groups. Only 1 of 31 (3.2%) patients in the controlled DOPBP group had an AE—an ischemic CVA. The prevalence of AEs increased within higher DOPBP groups: there were 7 (13.4%) events in the intermediate group and 12 (30%) events in the high group. The average INR 2 weeks before ICH was 2.2 (range, 1.2–5.8; 1 patient was above the institutional goal of 2–3), and 2 weeks before TE it was 2.4 (range, 1.4–4.8; 3 patients were <2). There were 12 patients included with a centrifugal device and only 1 (8%) had an AE (ICH). In comparison, 19 of the 111 (17%) patient with an axial flow device had AEs (P=0.69).

Risk of ICH, TEs, and pAI

At the end of follow-up, there was a significant difference in the occurrence of the primary end point between DOPBP
Survival free from ICH, TE, or pAI at 18 months after CF LVAD implantation was 70% in the high DOPBP group, 86% in the intermediate, and 97% in the low DOPBP groups (P=0.004; Figure 2). Patients with a high DOPBP had an adjusted hazard ratio of 16.4 (95% confidence interval, 1.8–147.3; versus controlled DOPBP) and of 2.6 (95% confidence interval, 0.93–7.4; versus intermediate DOPBP) for the combined end point. When DOPBP was assessed as a continuous variable, patients with a combined end point had a significantly higher DOPBP of 90±10 in comparison with those without an event 85±10 (P=0.05).

Clinical Outcomes
Patient’s clinical outcomes with and without AEs are listed in Table 3. Six of 8 patients (75%) expired after an ICH, and the remaining 2 stayed on CF LVAD support. Of the 3 patients with an ischemic CVA, 1 expired, 1 underwent cardiac transplantation,
and the remaining patient was kept on CF LVAD support. Two of the 4 patients with pump thrombosis underwent emergent device exchange, whereas the other 2 patients had cardiac transplantation. No patients with pAI had any aortic valve interventions. Importantly, 103 (84%) patients did not have an ICH, TE, or pAI; of 103, 43 of them underwent cardiac transplantation, 47 remained on CF LVAD support, 3 underwent device exchange, and 10 eventually expired.

Discussion

The results of this study demonstrated that there is a graded association of blood pressure on a composite of AEs, including ICH, TEs, and pAI in patients supported by a CF LVAD. This was a contemporary cohort with a mean age of 57 years, 49% ischemic cause, 24% women with diligent follow-up in our LVAD clinic as reflected by their aggressive medical management: ≈90% were on a β-blocker, more than one half on angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and ≈approximately one third on a combination of hydralazine/nitrates. In the analysis, we demonstrated that patients with a mean DOPBP, within the guideline recommendation of <80 mm Hg, were remarkably free of AEs with only 1 of 31 subjects experiencing an event. The risk of an AE increased by DOPBP: the intermediate group (80–89 mm Hg) had an adjusted hazard ratio of 2.6 (P=0.06) which rose to 16.1 (P<0.012) in the high group (>90 mm Hg) in comparison with the controlled group. Secondary outcomes analysis of the individual end points demonstrated that this association was maintained for ICH and pAI. Such findings must be interpreted with an understanding that patients with a high DOPBP comprised a population with greater risk factors for AEs. Patients in the high DOPBP group had worse baseline renal function, lower usage of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and more prevalent history of hypertension in comparison with those in the intermediate and controlled groups. Notwithstanding such intrinsic risk factors, this is the first report to associate DOPBP with a composite of AEs in a CF LVAD population.

The significant design advantages offered by rotary pumps suggest that not only current but also all future generations of ventricular assist devices will use this mechanism for blood propulsion. These advantages present new challenges as well, a notable one being the creation of a distinct nonpulsatile...
dilatation as a consequence of the elevated pressure caused by the progressive aortic insufficiency. Although these hypotheses may appear evident, they have never previously been validated.

To mechanistically understand the association between blood pressure and AEs demonstrated in the present analysis, an examination of each individual end point is relevant. There is an established causal relationship between elevated blood pressure and ICH in normal pulsatile physiology. We hypothesized that the effect of a blood pressure elevated continuously throughout the cardiac cycle on the intracerebral vasculature may be even more detrimental. In our cohort, no patients with a controlled DOPBP experienced an ICH, whereas 6 of 40 (15%) patients with a DOPBP ≥90 mmHg had an event during the follow-up period. ICH was a devastating complication with 6 of 8 patients expiring. Furthermore, excluding events within the first 30 days after implant, ICH tended to occur early with a median time to event in the entire cohort of 69 (range, 31–226) days. These findings highlight the importance of early blood pressure control to prevent this serious complication.

Development of aortic insufficiency during CF LVAD support is common with freedom from AI at 1 year documented as ≈75%. Aortic valve closure seems to play a primary role in this process, and although the pathophysiology remains unclear, it is likely as a result of an increase in the duration of the instantaneous transvalvular pressure gradient leading to pathological remodeling and commissural fusion. Aortic root dilatation as a consequence of the elevated pressure caused by retrograde flow from the outflow cannula is also a contributing factor. Appropriately, much attention has been dedicated to pump speed operation for promotion of aortic valve opening to mitigate this complication. Less attention has focused on hypertension, which could potentially influence the aforementioned pathophysiology via increased aortic pressure and contribute to pAI.

<table>
<thead>
<tr>
<th>Combined end point</th>
<th>Univariable Hazard Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Intermediate vs controlled</td>
<td>4.213 (0.518–34.27)</td>
</tr>
<tr>
<td>High vs intermediate</td>
<td>2.727 (1.072–6.941)*</td>
</tr>
<tr>
<td>High vs controlled</td>
<td>11.455 (1.488–88.192)*</td>
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<table>
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<tr>
<th>Intracranial hemorrhage</th>
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<tbody>
<tr>
<td>Intermediate vs controlled</td>
<td>†</td>
</tr>
<tr>
<td>High vs intermediate</td>
<td>4.357 (0.878–21.615)</td>
</tr>
<tr>
<td>High vs controlled</td>
<td>†</td>
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<tr>
<th>Thromboembolic events</th>
<th></th>
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<tbody>
<tr>
<td>Intermediate vs controlled</td>
<td>1.77 (0.184–17.019)</td>
</tr>
<tr>
<td>High vs intermediate</td>
<td>1.607 (0.322–8.005)</td>
</tr>
<tr>
<td>High vs controlled</td>
<td>2.786 (0.289–26.849)</td>
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<tr>
<th>Progressive aortic insufficiency</th>
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<tbody>
<tr>
<td>Intermediate vs controlled</td>
<td>†</td>
</tr>
<tr>
<td>High vs intermediate</td>
<td>2.772 (0.506–15.193)</td>
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<tr>
<td>High vs controlled</td>
<td>†</td>
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CI indicates confidence interval. *P<0.05. †No comparison was possible because of no events in the controlled blood pressure group.

Table 3. Patient Outcomes With and Without Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Intracranial hemorrhage (n=8)</td>
<td>6 expired and 2 remained on CF LVAD support</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td></td>
</tr>
<tr>
<td>Ischemic CVA (n=3)</td>
<td>1 expired, 1 cardiac transplantation, and 1 remained on CF LVAD support</td>
</tr>
<tr>
<td>Pump thrombosis (n=4*)</td>
<td>2 device exchanges and 2 cardiac transplantations</td>
</tr>
<tr>
<td>Peripheral embolism (n=1)</td>
<td>Right coronary artery aspiration thrombectomy</td>
</tr>
<tr>
<td>Progressive aortic insufficiency (n=6)</td>
<td>All 6 underwent clinical monitoring, no aortic valve interventions</td>
</tr>
<tr>
<td>No ICH, TEs, or pAI (n=103)</td>
<td>43 cardiac transplantations, 47 remained on CF LVAD support, 3 device exchanges (2 driveline infections and 1 driveline fracture), and 10 expired</td>
</tr>
</tbody>
</table>

CF LVAD indicates continuous flow left ventricular assist device; CVA, cerebrovascular accident; ICH, intracranial hemorrhage; pAI, progressive aortic insufficiency; and TEs, thromboembolic events.

Patient Outcomes With and Without Adverse Events
both of the clinically approved devices, HeartMate II and HW, in our analysis. The afterload sensitivity of these pumps is different based on their axial versus centrifugal design and therefore, as previously noted, the effect of hypertension on the devices may be variable. This is a retrospective study, and we were limited to blood pressure readings obtained during clinic visits although it should be noted that we maintain close follow-up with our patients who are generally seen on a biweekly to monthly basis. Also, as is common to many LVAD analyses, the influence of center-specific management strategies may limit the generalizability of these findings. INR was not retrievable in patients without AEs, and thus it is not included in the multivariable analysis. However, the degree of anticoagulation is not likely to affect AEs because the average INR before AEs was within the therapeutic range. Patients with the highest DOPBP had worse renal function at baseline, which may have limited certain antihypertension therapies and is itself a marker of a worse prognosis. Finally, this was a small cohort with a low event rate, thereby limiting the use of multivariable modeling and requires confirmation in a larger population.

In conclusion, our data demonstrate that in a population at risk, there is a graded association between poor blood pressure control and AEs. Because the field of mechanical circulatory support moves to longer durations of support, this issue will become increasingly important. Further study in a larger population exploring this association, as well as the difference between centrifugal and axial flow design, and the efficacy of antihypertensive treatment is warranted.

Sources of Funding
This study was supported by intramural research funds.

Disclosures
Dr Goldstein serves as a consultant for Thoratec Inc. He also serves on the scientific advisory board of HeartWare and is their surgical director. He also serves on the scientific advisory board of HeartWare and is their surgical director. Also, as is common to many LVAD analyses, the influence of center-specific management strategies may limit the generalizability of these findings. INR was not retrievable in patients without AEs, and thus it is not included in the multivariable analysis. However, the degree of anticoagulation is not likely to affect AEs because the average INR before AEs was within the therapeutic range. Patients with the highest DOPBP had worse renal function at baseline, which may have limited certain antihypertension therapies and is itself a marker of a worse prognosis. Finally, this was a small cohort with a low event rate, thereby limiting the use of multivariable modeling and requires confirmation in a larger population.

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