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

Saeed et al: Blood Pressure and Adverse Events

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Abstract

Background—Adverse events such as intracranial hemorrhage (ICH), thromboembolism (TE) and progressive aortic insufficiency (pAI) create substantial morbidity and mortality during Continuous Flow Left Ventricular Assist Device (CF) LVAD 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 up to 18 months by a CF LVAD from June 2006 to December 2013 was conducted. All outpatient Doppler Blood Pressure (DOPBP) recordings were averaged up to the time of ICH, TE or pAI. DOPBP was analyzed as a categorical variable grouped as high (>90 mmHg, n=40), intermediate (80-90 mmHg, n=52) and controlled (<80 mmHg, n=31). Cumulative survival free from an AE was calculated using Kaplan–Meier curves and Cox hazard ratios (HRs) were derived. Patients in the high DOPBP group had worse baseline renal function, lower ACE inhibitor or ARB usage during CF LVAD support and a more prevalent history of hypertension. Twelve (30%) patients in the high DOPBP group had an AE, in comparison to 7 (13%) patients in the intermediate DOPBP group and only 1 (3%) in the controlled DOPBP group. The likelihood of an AE increased in patients with a high DOPBP (adjusted HRs [95% CI]: 16.4 [1.8-147.3], p=0.012 vs. controlled and 2.6 [0.93-7.4], p=0.068 vs. intermediate). Overall, a similar association was noted for the risk of ICH (p=0.015) and pAI (p=0.078) but not TE (p=0.638). Patients with an AE had a higher DOPBP (90±10 mmHg) in comparison to those without an AE (85±10 mmHg; p=0.05).

Conclusions—In a population at risk, higher DOPBP during CF LVAD support was significantly associated with a composite of adverse events.

Key Words: blood pressure, intracerebral hemorrhage, thrombus, aortic regurgitation, left ventricular assist device
Although heart transplantation (HT) 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. Due to exorbitant wait times and stringent eligibility criteria for HT, the number of people, both as bridge to transplantation (BTT) and destination therapy (DT), living for extended periods on LVAD support is on the rise. Current best estimates place the total number worldwide living with a LVAD at >7,000. 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 utilizing either centrifugal or axial propulsion. These designs offer significant advantages including pump miniaturization, silent operation, and most importantly, enhanced device durability. Since these pumps move blood from the left ventricle to the aorta throughout the cardiac cycle, they create a non-physiologic continuous blood flow pattern and are referred to as continuous flow (CF) CF LVADs. With reduced or absent arterial pulse pressure, traditional methods of non-invasive blood pressure measurements are unreliable. This limitation is overcome by utilizing 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 previously been shown to have excellent correlation to systolic blood pressure measurement via arterial line in CF LVAD subjects.

Of the most common significant adverse events associated with CF LVADs, 3 are potentially modulated by blood pressure. These are (1) intracranial hemorrhage, (2) thromboembolic events, and (3) development of aortic insufficiency. The recently published
ISHLT guidelines for Mechanical Circulatory Support acknowledge this potential by recommending that patients with nonpulsatile CF LVADs should have DOPBP goal of \( \leq 80\text{mmHg} \). 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 adverse events 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**

Pre-operative clinical information and baseline demographics were collected from medical charts. The analysis commenced at 30 days post implant and after hospital discharge. DOPBP recordings from all outpatient clinical visits were averaged up to the time of the following adverse events (AEs): 1) intracranial hemorrhage (ICH), 2) thromboembolic events (TEs), and 3) development of moderate or severe aortic insufficiency, hence forth 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. INR was retrieved at the time of ICH and TE.

**Definition of Adverse Events**

Intracranial hemorrhage was defined as the presence of hemorrhage noted on a head CT scan accompanied by neurological symptoms. Thromboembolic events included ischemic CVA, peripheral embolism or device thrombosis. Ischemic CVA was defined as the presence of acute cerebral infarction noted on a head CT scan accompanied by neurologic 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 three groups based on their average outpatient DOPBP: 1) high (≥90 mmHg), 2) intermediate (80-89 mmHg) and 3) controlled (<80 mmHg). The primary endpoint was the occurrence of any AEs. Secondary endpoints were the occurrence of each individual AE, including ICH, TEs, or pAI. If patients had more than one AE, then analysis of the primary endpoint was done with the time to the first AE and the time to each individual AE was used in the secondary endpoint analysis.
Statistical analysis

Data are displayed as means ± standard deviation. Baseline demographics were compared between patients in all three DOPBP groups by Analysis of Variance (ANOVA) for continuous variables and the chi-square test for categorical variables. Cumulative survival free from primary and secondary endpoints 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. P values of ≤0.05 were considered statistically significant. DOPBP was also compared as a continuous variable between patients with and without the combined endpoint by the Student’s t-test. Statistical analyses were conducted in SAS version 9.3 (SAS Institute, Cary, NC).

Results

Patient Characteristics

The study group was comprised of 123 patients who were supported by a CF LVAD for at least 30 days and met the inclusion criteria. Nearly half (49%) of the total cohort had an ischemic etiology of cardiomyopathy and 31% had atrial fibrillation. Table 1 demonstrates the clinical characteristics of these patients categorized into the three 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 beta blocker use was high and similar across the groups. ACE inhibitor and ARB
utilization decreased with each successive DOPBP group while 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 since BP is known to be artificially elevated especially acutely during a neurological episode.

Prevalence of Adverse Events (AEs)

Twenty (16%) patients in the entire group had a predefined adverse event 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 amongst the three 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 two weeks prior to ICH was 2.2 (range 1.2-5.8; 1 patient was above the institutional goal of 2-3) and two weeks prior to 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 out of the 111 (17%) patient with an axial flow device had AEs (p=0.69).
Risk of Intracranial Hemorrhage, Thromboembolic Events and Progressive AI

At the end of follow up, there was a significant difference in the occurrence of the primary endpoint between DOPBP groups. 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 (aHR) of 16.4 [95% CI: 1.8-147.3] (vs. controlled DOPBP) and of 2.6 [95% CI: 0.93-7.4] (vs. intermediate DOPBP) for the combined endpoint. When DOPBP was assessed as a continuous variable, patients with a combined endpoint had a significantly higher DOPBP of 90±10 in comparison to those without an event 85±10 (p = 0.05).

Both univariable HRs (Table 2) and survival analysis (Figure 2) showed a graded rise in the risk of composite AEs. In individual endpoint analysis by Kaplan Meier curves, survival free from ICH at 18 months was significantly lower in the high DOPBP group (85%) in comparison to intermediate (96%) and low (100%) DOPBP groups (p=0.015; Figure 2). There was no significant difference in survival free from TEs across DOPBP groups (p=0.638; Figure 2).

Proportionally fewer patients were free of pAI at 18 months in the high DOPBP group (90%) in comparison to intermediate (96%) and low (100%) DOPBP groups (p=0.078; Figure 2).

Clinical Outcomes

Patient’s clinical outcomes with and without adverse events are listed in Table 3. Six out of eight patients (75%) expired after an ICH and the remaining two stayed on CF LVAD support. Of the three patients with an ischemic CVA, 1 expired, 1 underwent cardiac transplantation and the remaining patient was kept on CF LVAD support. Two of the four patients with pump thrombosis underwent emergent device exchange while the other two patients had cardiac
transplantation. No patients with progressive AI had any aortic valve interventions. Importantly, 103 (84%) patients did not have an ICH, TE or pAI and 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 adverse events including intracranial hemorrhage, thromboembolic events and progressive aortic insufficiency in patients supported by a CF LVAD. This was a contemporary cohort with a mean age of 57, 49% ischemic etiology, 24% female with diligent follow up in our LVAD clinic as reflected by their aggressive medical management: almost 90% were on a beta blocker, more than ½ on ACE inhibitor/ARB, and approximately 1/3 on a combination of hydralazine/nitrates. In the analysis, we demonstrated that patients with a mean DOPBP, within the guideline recommendation of <80mmHg, 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 (80-89mmHg) had an aHR of 2.6 (p=0.06) which rose to 16.1 (p<0.012) in the high group (>90mmHg) in comparison to the controlled group. Secondary outcomes analysis of the individual endpoints 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 ACE inhibitors or ARBs, and more had a history of hypertension in comparison to those in the intermediate and controlled groups.
Notwithstanding such intrinsic risk factors, this is the first report to associate DOPBP with a composite of adverse events 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 utilize this mechanism for blood propulsion. These advantages present new challenges as well, a notable one being the creation of a distinct non-pulsatile circulatory physiology. In patients with a CF LVAD, measurement, impact on outcomes, and target ranges for treatment of blood pressure currently lack clarity. Therefore, in the current analysis, we sought to define DOPBP goals in CF LVAD subjects by exploring the potential impact of blood pressure on adverse events. In particular, blood pressure could theoretically have a unique contribution to the development of ICH, thromboembolic events, and aortic insufficiency. Although these hypotheses may appear evident, they have never previously been validated.

In order to mechanistically understand the association between blood pressure and adverse events demonstrated in the present analysis, an examination of each individual endpoint is relevant. There is an established causal relationship between elevated blood pressure and ICH in normal pulsatile physiology.\textsuperscript{5} We hypothesized that the effect of a blood pressure elevated continuously throughout the cardiac cycle on the intra-cerebral 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 \( \geq 90\)mmHg had an event during the follow-up period. ICH was a devastating complication with 6 of 8 patients expiring. Furthermore, despite 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 one year documented as approximately 75%.\textsuperscript{6,7} Aortic valve closure appears to play a primary role in this process and while 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.\textsuperscript{8,9} Aortic root dilatation as a consequence of the elevated pressure caused by retrograde flow from the outflow cannula is also a contributing factor.\textsuperscript{10} 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. We found a strong trend towards increased pAI with higher DOPBP: none of the patients in the controlled DOPBP group while 4% in the intermediate group and 10% in the high group developed moderate to severe AI (p=0.078) during follow up. Importantly, the progression occurred late at a median of 347 (range: 102-513) days emphasizing the importance of persistent blood pressure control during extended support.

In the secondary endpoint analysis, a greater proportion of patients had TE events in the high (7.5%) and intermediate (5.8%) compared with the controlled group (3.2%) but this did not reach statistical significance. We had hypothesized that higher blood pressure by increasing afterload on the pump would reduce pump flow and increase propensity for device thrombus that could manifest as either embolic events or pump malfunction. A similar hypothesis had previously been validated in an analysis of the HeartWare ADVANCE bridge to transplant trial where elevated blood pressure increased the risk of pump thrombus.\textsuperscript{11} Our discordant findings from the HW analysis may be explained by the high proportion of the axial flow HMII (90%) in our study. Centrifugal pumps, such as the HW, are known to be more afterload sensitive and
therefore will have a greater reduction in pump flow in response to hypertension. The variable clinical impact of blood pressure on the HMII and HW raise important questions that need to be answered in a larger population.

There are several limitations to the current study that are worth addressing. First, patients with a high DOPBP also had demographic characteristics which may have put them at a higher risk of having an AE, thereby mitigating some of the risk attributed to DOPBP control. Second, we chose to include both of the clinically approved devices, HMII and HW, in our analysis. The afterload sensitivity of these pumps is different based upon their axial versus centrifugal design and therefore, as previously noted, the effect of hypertension on the devices maybe 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 impact AEs because the average INR prior to AEs was within the therapeutic range. Patients with the highest DOPBP had worse renal function at baseline, which may have limited certain anti-hypertension therapies and is itself a marker of a worse prognosis. Finally, this was a small cohort with a low event rate, thereby limiting the utility of multivariable modeling and requires confirmation in a larger population.

In conclusion, our data demonstrates that in a population at risk, there is a graded association between poor blood pressure control and adverse events. As 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.

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Disclosures

Dr. Goldstein serves as a consultant for Thoratec Inc. He also serves on the scientific advisory
board of HeartWare and is their surgical proctor.

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Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>CF LVAD type</th>
<th>Controlled (&lt;80 mmHg) n=31</th>
<th>Intermediate (80-90 mmHg) n=52</th>
<th>High (≥ 90 mmHg) n=40</th>
<th>Total n=123</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Axial</strong>, n (%)</td>
<td>28 (23)</td>
<td>47 (38)</td>
<td>36 (29)</td>
<td>111 (90)</td>
<td>0.927</td>
</tr>
<tr>
<td>rotor speed (rpm)</td>
<td>8981±414</td>
<td>8927±298</td>
<td>8950±293</td>
<td>8948±327</td>
<td>0.810</td>
</tr>
<tr>
<td><strong>Centrifugal</strong>, n (%)</td>
<td>3 (2)</td>
<td>5 (4)</td>
<td>4 (3)</td>
<td>12 (9)</td>
<td>0.875</td>
</tr>
<tr>
<td>rotor speed (rpm)</td>
<td>2710±70</td>
<td>2788±198</td>
<td>2834±84</td>
<td>2797±144</td>
<td>0.570</td>
</tr>
</tbody>
</table>

**=medications were retrieved at the time of an adverse event or at the end of follow up; LVEDD=left ventricular end diastolic diameter; LVEF=left ventricular ejection fraction; ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; GIB=gastrointestinal bleeding; **All Heart Mate II; *** All HVAD.
Table 2. Univariable hazard ratio estimates for the risk of an adverse event

<table>
<thead>
<tr>
<th>Doppler blood pressure group</th>
<th>Univariable hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combined Endpoint</strong></td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td><strong>Intracranial Hemorrhage</strong></td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td><strong>Thromboembolic events</strong></td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td><strong>Progressive Aortic Insufficiency</strong></td>
<td></td>
</tr>
<tr>
<td>Intermediate vs. controlled</td>
<td>*</td>
</tr>
<tr>
<td>High vs. intermediate</td>
<td>2.772 (0.506 – 15.193)</td>
</tr>
<tr>
<td>High vs. controlled</td>
<td>*</td>
</tr>
</tbody>
</table>

*p≤0.05; **=no comparison was possible due to 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>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial Hemorrhage (n=8)</td>
<td>6 expired, 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, 1 remained on CF LVAD support</td>
</tr>
<tr>
<td>Pump thrombosis (n=4*)</td>
<td>2 device exchanges, 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, 1 driveline fracture), 10 expired.</td>
</tr>
</tbody>
</table>

*=1 patient’s presentation for pump thrombosis was an ischemic CVA.
Figure Legends

**Figure 1.** Figure 1: (A) Distribution of combined and individual adverse events across blood pressure groups. (B) Distribution of the type of thromboembolic events across blood pressure groups.

**Figure 2.** Kaplan Meier curves showing the survival free from adverse events.
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