Blood Pressure Control in Continuous Flow Left Ventricular Assist Devices: Efficacy and Impact on Adverse Events

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Background. Continuous flow (CF) left ventricular assist devices (LVAD) are afterload sensitive and therefore pump performance is affected by hypertension. In addition, poorly controlled hypertension may increase the risk of aortic insufficiency (AI) and stroke. Blood pressure regimens after CF LVAD have not been studied and their impact on rates of AI and stroke are unknown.

Methods. Patients who had CF LVAD at a single center and were supported greater than 30 days were included. Blood pressure was monitored at home by Doppler. Outpatient management of blood pressure was conducted according to a predefined institutional protocol (target mean arterial pressure £ 80 mm Hg).

Results. A total of 96 patients were included. At the end of follow-up, 25 patients were not on an antihypertensive drug, of these 9 died. Of the 74% receiving antihypertensives, 54% required 1 medication, 34% were on 2, 10% were on 3, and 3% were on 4 or more. Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (85% of patients on an antihypertensive) and beta blockers (30%) were the most commonly prescribed medications. There was a significantly higher neurologic event rate in those on no antihypertensives compared with those on antihypertensives ($p = 0.009$). Only 3% of patients with no or mild AI at baseline progressed to develop moderate or greater AI after a mean of 201 days of follow-up.

Conclusions. Blood pressure control can be achieved in patients with CF LVADs, with the majority of patients requiring only 1 or 2 antihypertensives.
laboratory data, adverse events, and pump parameters entered prospectively into the Transplant Patient Management System (TPMS) database. All patients consented to their participation in the TPMS database and the University of Pittsburgh Institutional Review Board approved the study.

The study included all patients who underwent implantation of a CF LVAD between January 1, 2006 and October 15, 2011, and who were supported at least 30 days. Patients were followed through December 31, 2012. Our database was retrospectively reviewed to obtain data for this investigation. All blood pressures obtained during the implant hospitalization were obtained by the inpatient nursing staff using a Doppler probe. Prior to discharge, the patient and their caregivers were trained to obtain their BP with a Doppler probe. The opening BP was considered the mean pressure for the purpose of the study. All blood pressures, along with the corresponding device parameters at the time of measurement were entered into the TPMS database. All medications and doses were also prospectively entered into the database. Outpatient management of BP was conducted according to a predefined institutional protocol (Fig 1) with a target mean pressure of 80 mm Hg. Blood pressures were averaged for each person over months 1, 2, 3, 4, 5, and for 6 months and beyond. The final antihypertensive medications at the end of follow-up was the last outpatient regimen for those patients who died or were transplanted, and the last recorded outpatient antihypertensive regimen for those remaining on support.

All adverse events were recorded according to the Interagency Registry for Mechanically Assisted Circulatory Support adverse event definitions [9]. The pretransplant degree of aortic insufficiency (AI) was recorded from the echocardiogram performed closest to the time of MCS. The final degree of AI was determined by the echocardiogram closest to the end of follow-up, transplantation, or death. Renal function was determined by the modification of diet in renal disease (aMDRD) formula and averaged for each person over months 1, 2, 3, 4, 5, and for 6 months and beyond. Obesity was defined as a body mass index of greater than or equal to 30 kg/m².

**Statistical Analysis**

All continuous variables were compared across patient subgroups (eg, patients receiving axial versus centrifugal MCS; patients receiving no antihypertensives versus 1
medication versus 2+ medications) with F tests and t tests for normally distributed variables; otherwise a Kruskal-Wallis test was utilized. Categoric variables were compared with the χ² or Fisher exact test. The cumulative incidence of neurologic events during the first year of MCS support (accounting for censoring due to death or transplantation) was examined as a function of the number of antihypertensives prescribed (0, 1, or 2+ medications) using Kaplan-Meier analysis and Breslow method. Freedom from more than mild AI was compared by number of antihypertensives for patients with mild or less AI at the time of implant and did not have an aortic valve intervention using Kaplan-Meier analysis.

Results
A total of 108 patients were implanted with a CF LVAD during the study period, 96 of whom were supported over 30 days and included in the final analysis. A total of 12 patients were excluded due to support time of 30 days or less; 8 with a HeartMate II (Thoratec, Pleasanton, CA) (4 deaths, 1 weaned, 3 ongoing) and 4 with a HeartWare (HeartWare International, Inc, Framingham, MA) (1 transplanted, 3 ongoing). Of the 96 CF LVADs, there were 59 HeartMate II, 22 Ventracor (Ventracor, Sydney, Australia), 13 HeartWare, and 2 Jarvik 2000 (Jarvik Heart, Inc, New York, NY). Overall, patient demographics are similar to most studies of MCS with a mean age of 55 years, 80% male, and 79% white, and the etiology of heart failure was ischemic in 50% (Table 1). Overall incidence of pre-implant hypertension was 67%, with a trend toward a higher pre-implant incidence of hypertension in the axial flow group. The pre-implant incidence of diabetes was similar; however, body mass index was higher in the axial flow group. There were more axial flow LVADs implanted as destination therapy than centrifugal flow pumps (51% vs 23%, p = 0.003) consistent with availability of devices for this indication during the study period. Given this, mean duration of support was also longer in the axial flow devices (316 vs 168 days, p = 0.009).

The mean number of BP values obtained per patient over their duration of support was 318. At the end of follow-up, 25 patients were not on antihypertensives, of these 9 (36%) died; whereas, of the 71 patients on at least 1 antihypertensive, only 12 (17%) died. The causes of death were diverse and there were no significant differences in cause of death based upon the number of antihypertensives (Table 2). Of the 74% receiving antihypertensives, 54% required 1 medication, 34% were on 2, 10% were on 3, and 3% were on 4 or more. There was no difference between axial and centrifugal flow devices in the percentage of patients requiring antihypertensives. As per protocol, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers were the most commonly prescribed medications, used in 85% (n = 60) of those on therapy (Table 3). Lisinopril was the most frequently used angiotensin-converting enzyme inhibitors (n = 53) with a mean dose of 20 mg. Beta blockers were used in 30% (n = 21) of patients, with carvedilol used most commonly (n = 20) with a mean daily dose of 27 mg. Calcium channel blockers were the next most utilized in 28% (n = 20) with amlodipine used in all but 1 patient. Alpha blockers were used in 21% (n = 15), all of which were on clonidine.

When assessed by month post implant, overall BP control was near goal and not significantly different between axial and centrifugal devices over the first 5 months.
of support (Fig 2). Beyond month 6, the mean BP in centrifugal flow pumps was lower than axial flow pumps (80 vs 85 mm Hg, \( p = 0.03 \)), but only 13 patients remained on support with centrifugal flow pumps. Mean pump flow at each monthly interval was also not significantly different between axial and centrifugal flow pumps (Fig 3). Overall mean pressure for those on no antihypertensives was 75.5 mm Hg and was significantly lower than those on 1 medication or 2 or more medications; 81.4 and 82.7 mm Hg, \( p = 0.0001 \). During each of the first 6 months of support, with the exception of month 5, patients on no antihypertensives had a lower BP than those on an antihypertensive (Fig 4). There were no differences in baseline demographics between those not on an antihypertensive versus those who were: age 58 versus 55 years, \( p = 0.25 \); male 80% vs 80%, \( p = 0.98 \); white 84% vs 78%, \( p = 0.50 \); bridge to transplant 60% vs 59%, \( p = 0.94 \). The pre-implant presence of hypertension was not higher in those who required post-LVAD antihypertensives, than those who did not (69% vs 63%, \( p = 0.55 \)). Furthermore, there was no difference in the baseline incidence of diabetes (37% vs 35%, \( p = 0.84 \)) and obesity (48% vs 80%, \( p = 0.50 \)) for those who did and did not require post-LVAD antihypertensives.

At baseline, there were no differences in creatinine clearance between groups based upon the number of antihypertensives. During the first month of support the group not requiring an antihypertensive had a significantly lower creatinine clearance than those who required antihypertensives (53.2 vs 63.8 vs 60.1 mL/min/1.73 m², respectively, \( p = 0.04 \)). Beyond the first month, all groups had mild improvement in their renal function during the second month on support and a slow decline thereafter, but without significant differences among the 3 groups (Fig 5).

There were 31 neurologic adverse events in 23 patients; 6 patients had 2 events and 1 patient had 3 events. Of these events, there were 20 strokes and 11 transient ischemic attacks. All events occurred within 12 months of implantation. Of the 20 strokes, 16 were ischemic and 4 were hemorrhagic. There was no correlation between the number of antihypertensives required and hemorrhagic stroke, with 2 events in patients not on antihypertensives and 2 events in patients who required antihypertensives. The overall cumulative incidence of neurologic adverse events varied significantly by whether patients were taking no antihypertensives, 1 antihypertensive, or 2 or more medications (Breslow method \( = 9.82, p = 0.007 \)) (Fig 6). Additional pairwise comparisons indicate that the incidence of neurologic adverse events was significantly higher for those on no antihypertensives compared with each of the 2 groups who were on antihypertensives (\( p = 0.035 \) and 0.005 for the group on 1 medication and the group on 2+ medications, respectively). In patients who needed antihypertensives, the number of medications used was not associated with a significant difference in the rates of neurologic adverse events.

Almost all patients (90 patients, 94%) had either no or mild AI prior to LVAD implantation. The remainder of the patients had no more than mild to moderate AI. Of those with no or mild AI at implant, only 3% developed moderate or greater AI after a mean support of 201 days (Fig 7). Additionally, for those patients with mild or less AI at implant the freedom from developing greater than mild AI was 86% at 6 months and 83% at 1 and 2 years. Two-year freedom from more than mild AI was lowest in

### Table 3. Antihypertensive Drugs and Mean Doses

<table>
<thead>
<tr>
<th>Antihypertensive Class</th>
<th>No.</th>
<th>Drug</th>
<th>Dose (mg) Mean (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE/ARB</td>
<td>60</td>
<td>Lisinopril</td>
<td>53 20 (2.8–80)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>21</td>
<td>Carvedilol</td>
<td>20 27 (6.25–125)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>20</td>
<td>Amlodipine</td>
<td>19 8.7 (5–10)</td>
</tr>
<tr>
<td>Alpha blocker</td>
<td>15</td>
<td>Clonidine</td>
<td>15 0.7 (0.1–2.4)</td>
</tr>
</tbody>
</table>

ACE/ARB = angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers.
the group who did not require antihypertensives in comparison with those who required 1 or 2+ antihypertensives (92% vs 86% vs 75%, respectively), however these differences did not reach statistical significance (Fig 8).

Comment

Despite the importance of appropriate BP control in MCS patients and recommendations for its treatment, limited information exists regarding effective medication regimens and monitoring protocols [10, 11]. Current guidelines for outpatient management of hypertension in patients with CF LVADs only endorse a preference for heart failure medications [10].

Our study demonstrates that most patients with CF LVADs will require medical management of hypertension. Of those patients who did not die on while on support, 87% required at least 1 antihypertensive and over 80% of those patients were managed on only 1 or 2 medications. There was not a higher prevalence of treated hypertension by the presence or absence of pre-implant hypertension. As per our institutional protocol, angiotensin-converting enzyme inhibitors and beta blockers were the most frequently used medications and were needed in moderate doses. Blood pressure was significantly lower in patients not on antihypertensives, but good BP control was achieved in patients who required medical management. There were no significant differences in the need for antihypertensives or the mean BP per month between those with axial or centrifugal flow devices. In terms of end-organ function, beyond 1 month there was no difference in the renal function between those who were on antihypertensives versus those who were not. The cumulative rates of neurologic adverse events were lower for those who were on antihypertensives and for those on therapy there was no difference in the rates of neurologic events based upon the number of medications needed to control BP. There was also a low rate of development of, or progression to, greater than mild AI.
Chronic management of hypertension in patients with LVADs can present unique challenges. Because patients with CF LVADs often do not have a palpable pulse, traditional BP measurement by auscultation or automated cuff is less reliable. However, Doppler ultrasound measurements have been shown to detect a pressure in almost all patients and to reliably correlate with arterial catheter mean arterial pressure [12]. Our study also demonstrates that patient-directed chronic Doppler monitoring of BP can be easily established, although data on degree of compliance with BP measurement were not available. Additionally, we demonstrated that a pre-defined BP management protocol was effective and useful in directing a consistent approach to hypertension management. The protocol used in our institution focuses on using heart failure medications for BP control as recommended in the International Society for Heart and Lung Transplantation Mechanical Circulatory Support Guidelines and may easily be adopted.

Continuous flow LVADs generate a specific flow for a given pressure differential across the pump; as a result, they are both preload and afterload-dependent, making BP control essential. Axial and centrifugal CF pumps show similar relationships between pressure and flow; at a constant pump speed as the pressure differential across the pump increases (increased afterload, decreased preload), the pump output decreases. Likewise, a decrease in the pressure differential (decreased afterload, increased preload) leads to increased pump output. Although both axial and centrifugal flow pumps are afterload dependent, the pressure to flow relationship of centrifugal flow pumps tends to be substantially less steep than of axial flow pumps; thus, for any change in afterload there is a greater change in flow for centrifugal flow pumps. As such, hypertension management may be particularly important in centrifugal flow devices. Despite this, our study did not demonstrate any differences in clinical outcomes between pump types, which may reflect the similar degree of BP control in our axial and centrifugal flow devices. The focus on afterload in order to maximize the unloading of the left ventricle has important clinical implications not only for pump function and symptomatic benefit, but also in the setting of pulmonary hypertension. For patients with high pulmonary vascular resistance due to chronic heart failure, adequate unloading is critical to allow the best opportunity to improve pulmonary resistance. Such patients require optimization of their afterload to achieve and maintain low left ventricular filling pressures.

Neurologic events can be the most significant adverse event associated with MCS, affecting functional status, quality of life, and survival. Minimizing the risk of
neurologic events is even more important as MCS is contemplated in a less sick population of patients. The cumulative rate of neurologic events was higher in our patient population who were not on antihypertensives; however, in those patients needing antihypertensives, the number of medications was not associated with an increased cumulative incidence of neurologic events. Moreover, there was no correlation between hemorrhagic stroke and the number of antihypertensives or use of a centrifugal device. The higher cumulative rates of stroke and transient ischemic attacks in those who did not require antihypertensives may relate to the effect of an early neurologic event on the subsequent need for BP control. Alternatively, the patients not on antihypertensives at the end of follow-up may have had comorbidities contributing to both a lower BP and increased risk of neurologic events. In particular, while there was no difference beyond 1 month, patients not on an antihypertensive had lower creatinine clearance at 1 month post implant which may reflect a more difficult perioperative course that put them at risk for future events. However, the overall lower rate of neurologic events in those who required antihypertensives seems to reinforce the need for adequate BP control in those who are hypertensive. The lack of difference in the cumulative rates of neurologic adverse events for those on 1 versus 2 or more antihypertensives and the similar achieved BP between the 2 groups suggests the degree of control impacts the rates of events rather than the number of medications required for treatment. The optimal range of BP control and whether a different target BP goal would decrease the rate of neurologic events requires further study.

Hypertension can worsen preexisting AI or lead to de novo AI in the setting of a closed aortic valve or one that rarely opens. In a small series of paired aortic root samples from patients on MCS, the aortic root demonstrated increased smooth muscle disorientation and depletion, increased fibrosis, greater degrees of cystic medial degeneration, and atherosclerosis at the end of support, which may contribute to the development of AI [13]. In another study of patients supported to 18 months over half of patients developed moderate or greater AI [14]. Development of AI compromises pump function as a proportion of the cardiac output delivered to the ascending aorta regurgitates back into the left ventricle and then back through the pump, creating a blind loop of flow not contributing to systemic perfusion. If AI becomes severe, it can lead to recurrent heart failure symptoms and necessitate aortic valve replacement [15]. While some controversy remains, published guidelines recommend treatment of hypertension in asymptomatic patients without MCS who develop AI in the setting of hypertension [16]. Thus, in addition to its effect on pump performance, effective BP control may mitigate some of the changes in the aortic root and valves previously demonstrated with long-term MCS. With aggressive BP control,
rates of development of, or progression to, more than mild AI in our study was lower than prior published series [14].

Limitations

Our observations and conclusions should be evaluated recognizing the inherent limitations of a retrospective review of prospectively collected data. All patients had the same BP control regimen and goal, so we do not know the impact of a more or less aggressive regimen on pump performance, BP control, or adverse events. The categorization of a patient’s need for antihypertensives was based upon their use at the time of transplant or their last outpatient follow-up. While many patients who were categorized into the group not on antihypertensives did not require them throughout the duration of support, some had intermittently been on antihypertensives prior to their discontinuation. The use of the Doppler opening pressure measurements may overestimate the mean BP in the centrifugal group more than the axial pump group because of the increased pulsatility in centrifugal pumps. The length of pump support varied, mostly with the percentage of patients implanted as destination therapy, and the rate of adverse events over a longer period of support remains unknown. However, the rates of neurologic adverse events were highest in the first 6 months after implant surgery and given the mean duration of support the impact of BP control on neurologic events beyond 1 year is unclear. In contrast, the development of AI may become more pronounced with long-term support and the length of follow-up in the current study may not have been sufficient to determine the true rates of AI. Additionally, the patient population was relatively small and performed at a single center, and these findings may not be applicable to the general population implanted with MCS.

Conclusions

Treatment of hypertension is important in the long-term management of patients with CF LVADs. Our study demonstrated that good BP control can be achieved in this patient population, with the majority of patients requiring only 1 or 2 antihypertensives. Effective BP control may impact the rate of adverse events such as AI and neurologic events. Refinement of the optimal regimen for such patients requires further study.

References

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