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Hypertension: An Unstudied Potential Risk Factor for Adverse Outcomes during Continuous Flow Ventricular Assist Device Support

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Abstract

In end-stage heart failure, left ventricular assist devices (LVADs) represent an exciting new frontier in which post-device-implantation survival approaches that of heart transplant. However, expansion of this technology is still limited by complications that impact morbidity and mortality. Thus, it is essential to identify and optimize modifiable predictors of poor outcomes. One such predictor may be hypertension (HTN). Not only may chronic HTN as a traditional cardiovascular risk factor be present during long-term LVAD support, but HTN may also contribute to device malfunction or device-associated complications. Although current guidelines identify blood pressure (BP) control as important to outpatient continuous flow (CF) LVAD management, there is no evidence base to support these guidelines. Indeed, our comprehensive literature search did not identify any studies that evaluated post-device-implantation HTN as a potential predictor of adverse CF-LVAD outcomes. Hypertension among CF-LVAD patients is likely a relatively unstudied factor because of difficulties using standard non-invasive techniques to measure BP in the setting of reduced pulsatile flow. Fortunately, recent research has elucidated the meaning of Doppler BP measurements and validated a slow-deflation cuff system for BP measurements in the setting of CF-LVAD support. Therefore, CF-LVAD researchers and clinicians may i) consider potential mechanisms relating HTN to poor outcomes, ii) realize that HTN management is a stated goal despite scarce evidence, and iii) utilize the new reliable and valid methods for outpatient BP measurement that make research and management possible. It is critical and now feasible that research on HTN in the CF-LVAD patient population move forward.

Keywords

hypertension; blood pressure; left ventricular assist devices; outcomes

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Introduction

The survival rate with current LVAD technology is approaching that of heart transplant. [1] Further improvement in LVAD survival stemming from evolving technology and management approaches may justify a future shift in triaging patients from transplant to destination therapy LVAD. In the meantime, LVAD complications negatively impact morbidity and mortality to an extent that limits such expansion of this technology. Pending technological advances, clinicians and researchers must continue to elucidate modifiable predictors of poor outcomes in order to optimize contemporary, continuous-flow (CF) LVAD management and thereby reduce morbidity and mortality.

Hypertension (HTN) is an established long-term risk factor for cardiovascular disease and may represent a risk factor for poor outcomes among CF-LVAD patients. Not only may HTN cause CF-LVAD dysfunction or contribute to CF-LVAD-associated complications but, additionally, chronic HTN, as a traditional cardiovascular risk factor, may negatively impact outcomes during long-term CF-LVAD support.[2, 3] However, there is little literature to provide an evidence base for HTN management among LVAD patients, mainly because of methodological challenges in its measurement due to reduced pulse pressure (PP).

The goal of this review is to describe the state of current knowledge regarding HTN as a prognostic factor among patients on CF-LVAD support.

Hypertension as a Potential Risk Factor among LVAD Patients

Hypertension may be a risk factor for poor outcomes among CF-LVAD patients by contributing to device dysfunction and device-related complications (Figure). The mechanisms involved reflect important hemodynamic and pathophysiologic consequences of CF-LVAD's unique physiology. Unlike in the setting of a pulsatile LVAD, afterload or systemic vascular resistance may greatly affect the amount of cardiac output support provided by a CF-LVAD.[3] Thus, poorly controlled BP may have detrimental consequences in LVAD patients for many different reasons. First, by decreasing CF-LVAD flow it may contribute to device thrombosis. Thrombosis itself may in turn lead both to device dysfunction resulting in worsening heart failure and to thromboembolism resulting in stroke as clots can propel through the device, embolizing systemically.[4] Second, by reducing CF-LVAD flow and ventricular unloading, poorly controlled BP may increase left ventricular filling pressures leading to worsening heart failure symptoms and eventually to hospitalization for hemodynamic optimization using intravenous diuretic and inotropic agents. Third, elevated right and left ventricular filling pressure may lead to stretch- and subendocardial ischemia-induced ventricular arrhythmias,[5] particularly among CF-LVAD patients with a history of pre-operative ventricular arrhythmias.[6] Finally, HTN may also promote de-novo aortic insufficiency (AI) among CF-LVAD patients, with increased afterload possibly contributing to decreased frequency of aortic valve opening, commissural fusion, and ultimately AI.[7, 8] Our recent CF-LVAD cohort analysis does not necessarily support this hypothesis that HTN might induce AI but our analysis of BP as a potential risk factor for AI was limited by the study's cross-sectional nature and few BP measurements.[9]

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With longer duration of LVAD support, patients can be also exposed to HTN as a traditional risk factor, as it exists among non-LVAD patients. The duration of LVAD support has extended considerably: 44% of adult, first-time mechanical circulatory support recipients are undergoing destination therapy device implantation and 10% undergo bridge-to-transplant implantation with only a “moderate” or “unlikely” chance of ever receiving a heart transplant.[10] Even patients with a higher likelihood of transplantation have progressively longer device duration because transplant wait list times are extending in several UNOS Regions and for blood type O patients in particular.[11] Therefore, with chronic support, exposure to traditional risk factors such as HTN is an important consideration.

Chronic, poorly controlled HTN can affect CF-LVAD patients in several ways. Sustained HTN can be linked with systemic complications such as vascular disease and bleeding.[2, 12] Hypertension can perpetuate and contribute to the deterioration of AI independently of aortic valve opening.[13] Additionally, HTN is a well-established risk factor for both ischemic and non-traumatic hemorrhagic stroke in non-LVAD patients.[14–16] Hemorrhagic stroke among CF-LVAD patients is of particular concern because the incidence rate is high, ranging from 0.05 (HeartMate, Thoratec)[17] to 0.09 (HVAD, HeartWare)[18] events per patient year, and it represents one of leading causes of CF-LVAD associated death.[19] Finally, poorly controlled HTN in the setting of anticoagulation – a standard of LVAD management – poses an even greater bleeding risk. Two scores – HAS-BLED and HEMORR$_2$HAGES – designed and utilized to assess bleeding risk among patients on anticoagulation (albeit with the clinical indication being atrial fibrillation rather than LVAD) both include uncontrolled HTN as an independent risk factor.[20, 21]

Hypertension as a Target in CF-LVAD Management

Manuscripts as well as current International Society for Heart and Lung Transplantation guidelines regarding the clinical management of LVADs identify HTN management as a specific component of post-implantation patient care, although specific BP goals for CF-LVAD patients vary slightly according to the publication.[2, 3, 22] Wilson et al. suggest a MAP goal of 70–90 mmHg[2] while Slaughter et al. suggest 70–80 mmHg.[3] International Society for Heart and Lung Transplantation guidelines advise a goal MAP <80 mmHg, but this recommendation is a Class IIb recommendation based on level of evidence C.[22] This guideline is based on expert panel consensus due to a lack of randomized studies regarding CF-LVAD patient care.[22]

An assessment of the extent of this evidence gap was warranted and, as such, we undertook a comprehensive literature search on HTN and outcomes among CF-LVAD patients. Indeed, our methodical search yielded minimal data, providing an important confirmation of the dearth of evidence on this topic. Our search is described below.

Methods and Results of a Literature Search on HTN and CF-LVAD Outcomes

A comprehensive search of the literature was conducted to identify studies relating HTN to adverse outcomes among CF-LVAD patients. Medline was searched through January 17,

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2014 with a search strategy based on a combination of three categories of keyword variations: 1) assist devices (heart/(left) ventricular/continuous flow assist device; 2) mechanical circulatory support, HeartMate); and 3) BP (BP, MAP, pulse pressure, systolic/systole), and outcomes (morbidity, mortality, survival/survival rate/survival analysis, post-operative complications, complications, adverse events, patient readmission/re-hospitalization). The search focused on English language studies of human subjects.

The search yielded 397 studies, of which one was relevant to the original search question. However, closer reading showed that it discussed only a single patient case.[23] The case study described a patient with poor device output in the setting of HTN, leading the authors to suggest that managing afterload in LVAD patients is an important clinical consideration.[23]

Other articles identified in the search were reviewed in detail, but they did not address the search question. Seven articles evaluated clinical outcomes among CF-VAD patients but were found to include only pre-LVAD implantation BP measurements[24, 25] or HTN diagnosis.[8, 26–29] Another four studies sought to predict which patients are most likely to be readmitted or survive post-CF-LVAD;[30–33] however, these analyses and risk scores focus nearly exclusively on pre-operative variables and none addressed post-operative BP or HTN or any other medically modifiable, post-operative predictors of outcomes.

Therefore, our comprehensive search did not identify any literature to inform an evidence-based summary on the potential contributions of HTN to CF-LVAD complications. One possible reason for the dearth of data on this important topic is the difficulty in measuring and interpreting BP in CF-LVAD patients.

Measuring BP in the Setting of LVAD Support for HTN Research and Management

Non-invasive BP measurement has been problematic with reduced pulsatile flow. Early generation LVADs incorporated pumps producing pulsatile flow, mimicking physiologic conditions for end-organ perfusion and producing readily measurable systolic blood pressure (SBP) and diastolic blood pressure (DBP). However, pulsatile technology has disadvantages, warranting newer generation CF LVAD designs. Contemporary CF-LVADs produce low-pulsatile flow that translates clinically into lower SBP, PP[34] and MAP[35] compared to those pressures produced by pulsatile devices.

Currently, the gold-standard for BP measurement among CF-LVAD patients is an invasive arterial line, which is not feasible in the outpatient setting.[36] Unfortunately, despite being accurate, traditional automated BP monitors only successfully obtain a BP measurement approximately 50% of the time due to reduced PP with CF-LVAD.[37] Alternatives include Doppler ultrasound with sphygmomanometer as well as newer cuff-based technologies.

Doppler is used by many LVAD centers, though it requires specific technical expertise and it produces a single measurement that has had unclear meaning.[36] To address this limitation, we recently compared arterial-line and Doppler BP measurements among 30 CF-LVAD in-

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patients to better understand what Doppler BP measurements represent.[38] We found that Doppler BP measurements most closely reflect arterial-line SBP but may also closely reflect MAP in cases of low PP (i.e., below the sample median).[38] Therefore, Doppler BP consistently represents SBP and only in situations of low PP should Doppler BP be used as a surrogate for MAP.

Despite this better understanding of Doppler BP measurements, the issue of technical expertise persists, rendering it impractical for use among inexperienced clinic staff or for home BP monitoring. Therefore, newer technologies such as the Terumo Elemano BP Monitor – a novel slow cuff deflation device – have been developed to provide an alternative, valid method of CF-LVAD BP monitoring that requires less technical expertise for obtaining traditional SBP and DBP measurements. Terumo Elemano measurements may closely reflect gold-standard arterial-line measurements: we found that the correlation between Terumo Elemano and arterial line was as high as 0.83 for SBP and as high as 0.75 for MAP.[38] Terumo Elemano underestimated SBP by 0.3 mmHg and MAP by 1.7 mmHg.

Thus, our data support the practice of first using Terumo Elemano to measure BP among CF-LVAD patients. We also suggest that if Terumo Elemano measurements are unsuccessful or inconsistent across multiple readings, Doppler should be used to measure SBP in this population.

Conclusion

Research on HTN among CF-LVAD patients is largely absent despite a reasonable and logical expectation that it is likely a risk factor for poor outcomes in this patient population. Expert-consensus guidelines do identify BP control as an important component of outpatient CF-LVAD management,[22] but these guidelines do not draw from an evidence base because there are no data available from original research studies on this topic, as demonstrated by our comprehensive literature search. The lack of research regarding HTN among CF-LVAD patients is likely driven by measurement difficulties using standard techniques in the setting of non-pulsatile flow.

Fortunately, recent advances in BP measurement methods for CF-LVAD patients have helped to elucidate the meaning of a Doppler BP measurement and to validate a novel slow-cuff deflation device for BP measurements,[38] raising the potential for future studies on HTN among CF-LVAD patients. From this perspective, important evidence may be added from the recently commenced and ongoing supplemental cohort of the ENDURANCE protocol, in which HVAD destination therapy CF-LVAD patients undergo BP management according to a predefined algorithm using Doppler and Terumo and are followed for clinical outcomes, with particular attention paid to neurological events. Other critical next research steps are to: 1) identify the best methods and strategies by which to measure, monitor, and manage BP in hospital, clinic and home settings; 2) establish an evidence-based normal and goal BP range for CF-LVAD patients – perhaps eventually different goals based on the type of CF device pump implanted (i.e., axial or centrifugal); and 3) determine whether HTN is in fact a predictor of CF-LVAD outcomes. Supported by such information, BP control could be an

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important element of impactful medical management among the growing population of end-stage heart failure patients with long-term CF-LVAD support.

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Abbreviations

AI	aortic insufficiency
BP	blood pressure
CF	continuous flow
DBP	diastolic blood pressure
HTN	hypertension
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
LVAD	left ventricular assist device
MAP	mean arterial pressure
PP	pulse pressure
SBP	systolic blood pressure

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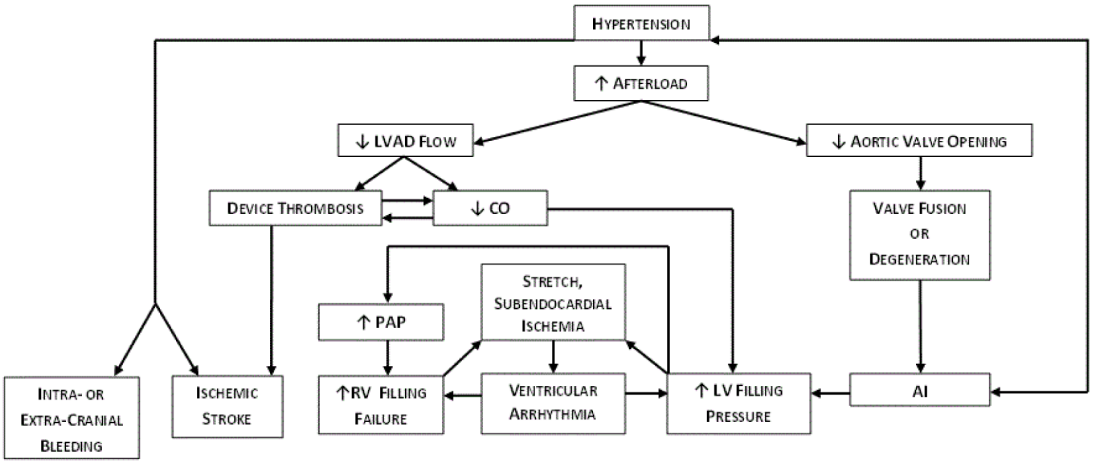

Figure.

Pathophysiological relationships between HTN and device-related complications in CF-LVADs.

AI = aortic insufficiency; CO = cardiac output; LV = left ventricular; PAP = pulmonary artery pressure; RV = right ventricular