The Effect of Left Ventricular Assist Devices (LVAD) on Pulmonary Hypertension in End-Stage Heart Failure.

by

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Abstract

Despite the increasing prevalence of advanced heart failure, transplantation rates have remained stable in Canada due to limited organ availability. Consequently, the number of implanted left ventricular assist devices (LVAD) and average time on device support have both risen rapidly.

End-stage heart failure is often complicated by pulmonary hypertension (PHTN). Patients with refractory PHTN have historically not been candidates for transplantation but reports of PHTN reversibility with LVAD support have led to changes to ISHLT listing criteria which now state that pulmonary hemodynamics should be reassessed 3 to 6 months following LVAD implantation for PHTN reversibility and transplantation candidacy.

All patients having received a durable LVAD at two transplantation institutions were included in our study. Pre-operative characteristics were obtained from institutional databases. Right-heart catheterization data was retrospectively retrieved for 90 days pre-insertion and up to death or loss of follow-up. Pulmonary vascular resistance (PVR) was calculated for each instance from the transpulmonary gradient and cardiac output. Generalized estimating equations and logistic regression were used to determine if any variables were associated with PHTN reversibility.

177 patients for a total of 790 hemodynamic measurements were captured. Patients with pre-operative PHTN were less likely to have an ischemic etiology but were otherwise similar to the normotensive cohort. In most instances, longitudinal PVR measurements for patients with and without pre-operative PHTN normalized by 6 months post-operatively. Additionally, in those patients who went on to transplantation, the pulmonary hypertension reversal experienced while on device support persisted post-transplantation.

Generalized estimating equation and logistic regression revealed that pre-operative PVR was the only clinical variable significantly associated with subsequent changes in PHTN.

In this study, LVAD use led to reversibility of PHTN for the majority of patients within 6 months. With the exception of pre-operative PVR, no other clinical variable was significantly associated with PHTN reversibility.

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1 Introduction

Left ventricular assist devices (LVAD) are surgically implanted mechanical pumps which supplement the failing heart's native cardiac output in cases of advanced heart failure. Once medical therapies have been exhausted, LVAD implantation and heart transplantation are the only two remaining therapeutic options for patients with end-stage heart failure. Given the rising prevalence of heart failure across Canada[1] and the relatively stagnant rates of heart transplantation due to limited donor organ availability[2], LVAD insertion rates have risen and developments in durable or long-term mechanical circulatory support technologies have grown considerably over the past decade to fill the emerging void in advanced heart failure therapy[3].

Pulmonary hypertension is a condition characterized by abnormally high blood pressures in the pulmonary circulation and right side of the heart. It is a potential complication of end-stage left-sided heart failure and, if refractory to medical therapy, has traditionally been a contraindication to heart transplantation. LVADs, in addition to treating the symptoms of heart failure and prolonging survival, may play a role in reversing the progression of pulmonary hypertension as has been suggested by recent case reports and series[4–7]. Despite this, very little is known with regards to the temporality and potential variables associated with this process.

We reviewed the medical records of patients having undergone LVAD implantation at the Maritime Heart Center (Halifax, NS) as well as the Brigham and Women's Hospital (Boston, MA) to examine the effect of LVAD implantation on reversibility of pulmonary

hypertension. Specifically, we examined pulmonary hemodynamic measurements over time to assess for changes in pulmonary hypertension as well as time-to-reversibility and attempted to identify pre-operative variables that may be associated with this process. The findings of this study will not only provide a greater understanding of the physiological changes that are associated with LVAD support at the level of the pulmonary vasculature but may also lead to more informed patient selection and tailored therapeutic approaches in the treatment of end-stage heart failure.

2 Background

2.1 Burden of Heart Failure in Canada

Heart failure is a clinical condition which results from volume congestion and decreased tissue perfusion in the setting of abnormal systolic and/or diastolic cardiac function[8]. It affects older Canadians at a higher rate, with data from 2012-2013 demonstrating that the incidence of diagnosed heart failure was 8.0 per 1,000 Canadian men aged 65-74 years, 21.0 per 1,000 men aged 75-84 and 44.5 per 1,000 for those aged 85 years or over. The incidence rates were slightly lower for Canadian women but still gradually increased with age: 5.4 per 1,000 women aged 65-74, 15.6 per 1,000 women aged 75-84 years, and 37.7 per 1,000 for those aged 85 years or over[9].

Heart failure represents a growing financial burden on our healthcare system. According to data from the Canadian Institute for Health Information's (CIHI) Discharge Abstract Database (DAD), there was a 25% increase in national hospitalization rates for heart failure from 2007 to 2017[10]. Stricter adherence to guideline-directed medical therapy and improved interventions in the management of ischemic heart disease are likely responsible for a decrease in the age-specific prevalence of heart failure as reported between 2004 to 2013[11]. However, given the aging Canadian population and the higher rates of heart failure observed in older age groups, the absolute number of inpatient admissions for the management of heart failure continues to increase. A recent publication has projected that annual numbers of admissions for heart failure would increase from 48,000 (95% CI 45,000-51,000) in 2020 to 54,000 (95% CI 49,000-60,000) by 2030. As the annual

admission costs per patient are expected to increase from an estimated $12,000 in 2020 to $14,000 in 2030, total admission costs are projected to increase by 49.8%, or a total of $722 (95% CI $650-$801) million, from 2013 to 2030[1]. Given these rapidly growing costs and the inherent financial contraints of the Canadian public healthcare system, judicious use of newer technologies and treatment strategies is warranted and thorough evaluation of the impact these interventions may have on patients should be undertaken prior to guideline modifications and widespread uptake.

2.2 Etiology and Natural History of Heart Failure

2.2.1 Pulmonary Hypertension in Heart Failure

Pulmonary hypertension is a condition which results from changes to the pulmonary vasculature and can be observed by elevations of the mean arterial blood pressure in the pulmonary circulation and subsequent physiologic changes.

The pathophysiologic changes associated with pulmonary hypertension secondary to heart failure have been well studied. In cases of left-sided heart failure, the initial event which leads to pulmonary hypertension is a passive transmission of increased pressure from an overloaded left ventricle to the pulmonary circulation[12]. In some patients, this additional mechanical load imposed by a failing left heart triggers a series of pathophysiologic changes in the pulmonary vasculature including pulmonary vasoconstriction, decreased nitric oxide production, overexpression of endothelin, diminished response to natriuretic peptide vasodilation and, finally, pulmonary arterial remodeling[13]. These effects eventually

lead to an elevation of the pulmonary vascular resistance (PVR) which may then result in increased right ventricular afterload and reduced right ventricular function[12].

2.2.1.1 Diagnostic Criteria of Pulmonary Hypertension in Heart Failure

Pulmonary hypertension was classically defined by two subtypes based on the presence or absence of identified causes or risk factors: primary pulmonary hypertension and secondary pulmonary hypertension[14]. As further research has gleaned more insight into this disease process, a more detailed classification has been proposed and refined by the World Symposium on Pulmonary Hypertension. The currently adopted classification divides pulmonary hypertension into five categories: pulmonary arterial hypertension (group 1), pulmonary hypertension due to left heart disease (group 2), pulmonary hypertension due to lung diseases and/or hypoxia (group 3), chronic thromboembolic pulmonary hypertension (group 4), and pulmonary hypertension with unclear or multifactorial mechanisms (group 5)[15]. Each broad classification can then be further divided based on the specific underlying etiology. Properly categorizing patients and their pulmonary hypertension is crucial as each may have specific underlying modifiable risk factors and therapeutic interventions and may carry category-specific prognoses.

2.2.1.2 The Natural History of Pulmonary Hypertension

Pulmonary hypertension is highly prevalent in patients with heart failure, and pulmonary hypertension secondary to left-sided heart disease is the most common etiology of pulmonary hypertension in these patients. An Italian study found that >60% of their

patients with moderate or severe heart failure met diagnostic criteria for pulmonary hypertension[16]. An exercise study of 320 patients with heart failure found that PVR was normal (<1.5 Woods Units (WU)) on invasive hemodynamic monitoring in 28%, mildly elevated (1.5–2.49 WU) in 36%, moderately elevated (2.5–3.49 WU) in 17%, and severely elevated (>3.5 WU) in 19% of the study subjects[17].

Pulmonary hypertension due to left-sided heart disease has also been associated with higher morbidity, poor quality of life, and increased mortality. A study of 108 patients with cardiomyopathy used tricuspid regurgitation (TR) on echocardiography as a surrogate for pulmonary hypertension and stratified patients as such when reporting clinical outcomes. At a mean follow-up of 28-months, they found that mortality was 57% in patients with a high TR velocity compared with 17% in patients with a low TR velocity (difference of 40%, 95% Cl, 20% to 60%). Additionally, hospitalizations for symptoms of heart failure occurred in 75% of those with higher degrees of TR compared to 26% in those with lesser TR (difference of 49%, Cl, 30% to 68%)[18].

2.3 Therapeutic Interventions in Heart Failure

2.3.1 Orthotopic Heart Transplantation

Heart transplantation remains the gold standard therapeutic modality for end-stage heart failure. When medical and traditional surgical interventions have been exhausted and patients remain symptomatic with heart failure, unacceptable quality of life and poor anticipated survival, an evaluation for heart transplantation candidacy is appropriate. As per the Canadian Cardiac Transplant Network[19], this would typically include patients with:

- Late-stage heart failure due to any cause
- Refractory life-threatening arrhythmias despite optimal medication, surgical, and device therapy
- Refractory angina not amenable to further revascularization
- Complex congenital heart disease with failed surgical palliation or not amenable to surgical palliation at acceptable risk

Once patients are deemed appropriate recipient candidates, they are then listed on a nationwide database and prioritized based on biological compatibility as well as disease severity and likelihood of survival without transplantation.

2.3.1.1 Contraindications to Heart Transplantation

Certain medical conditions portend a worse prognosis following heart transplantation, either because they increase the peri-operative risk associated with the procedure or because they limit the life expectancy of the recipient. Given the limited number of available organs, numerous relative contraindications have been developed by various representative bodies. The Canadian Cardiac Transplant Network's 2012 Eligibility and Listing Criteria lists the following as relative contraindications to heart transplantation: pulmonary hypertension, age over 70 years, obesity (defined as a BMI > 30kg/m^2), malignancy, diabetes with end-organ damage, renal dysfunction, peripheral vascular disease, tobacco and substance abuse, active infection, psychosocial issues, severe pulmonary or liver disease, immuno-incompatibility, ABO-incompatibility, and fetal

listing. Of note, given that these are all relative contraindications, the decision of whether to list a patient for candidacy is made on an individual-by-individual basis by cardiac transplant teams.

2.3.1.2 Organ Availability

Despite an increasing prevalence of advanced heart failure, transplantation rates in Canada have remained stable for the last decade due to the limited availability of suitable donor hearts (Figure 1). Data from the United States has revealed a recent increase in organ availability which has been attributed to the ongoing opioid crisis but Canadian rates have largely remained unchanged[20].

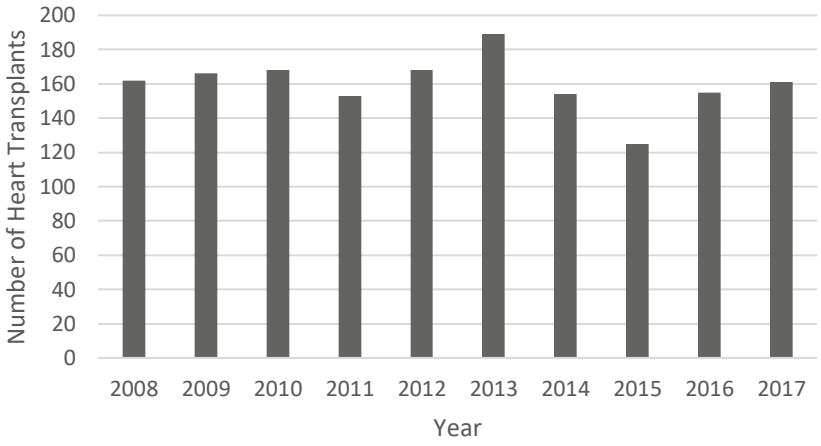

Figure 1: Transplantation rates for Canada per year (Data from Canadian Institute for Health Information's Organ Replacement Register)

Spain is a world-leader in solid organ transplantation rate since the country adopted legislation mandating voluntary opt-out for organ donation[21]. The province of Nova Scotia

has recently put forth a similar law[22], but it remains to be seen whether this will have a significant impact on provincial and national transplantation rates.

2.3.1.3 Prognosis Following Heart Transplantation

Since its inception in 1982, the International Society for Heart and Lung Transplantation (ISHLT) has prospectively gathered observational data on all patients undergoing heart transplantation at participating centers. According to their most recent annual report, the median survival time for adult heart transplant recipients is about 12 years[23]. Despite continuous improvements in prognosis following transplantation, survival rates remain lower than those of the general population. The most common causes of death following heart transplantation depend on the amount of time that has elapsed since transplantation. In the thirty days following implantation, early graft failure remains the leading cause of death while infection-related deaths are most common in the first year. Over the long-term, malignancy, chronic allograft vasculopathy and renal failure are the most prevalent causes of death[23].

2.3.2 Mechanical Support Devices

2.3.2.1 Left Ventricular Assist Device

Left ventricular assist device (LVAD) is a term used to describe surgically implanted mechanical pumps which serve to increase the native heart's cardiac output and that may be used in advanced heart failure. The early generations of LVADs were extracorporeal, bulky, and associated with significant adverse event profiles, rendering their long-term use

impractical. Newer generations of these devices have adopted much smaller profiles, and technological advances have significantly decreased their complication and adverse event rates. This has led to their increased use and patients being able to remain on device support for extended periods of time. The smaller profiles of newer generation LVADs have also allowed for the intracorporeal implantation of the device, with only a power driveline exiting the skin, thus allowing patients to leave hospital and lead relatively normal lives while on device support.

2.3.2.2 Mechanical Circulatory Support Strategies

Mechanical circulatory support, specifically LVAD implantation strategies, have been stratified into five different categories which are widely recognized in the heart failure literature and by the International Society for Heart and Lung Transplantation. These 5 strategies are as follows:

- Bridge to Decision *(LVAD inserted when the final treatment decision remains undetermined)*
- Bridge to Recovery *(LVAD inserted with the hope that myocardial function will recover sufficiently to allow for eventual explant of the device)*
- Bridge to Transplantation *(LVAD inserted in transplantation candidates who require an intervention but have not yet received a donor heart)*
- Bridge to Candidacy *(LVAD inserted in patients who do not currently meet transplantation eligibility criteria but who may qualify following device implantation and resuscitation)*

- Destination Therapy *(LVAD inserted in patients who are not expected to be eligible for transplantation and who will likely remain on mechanical support for the remainder of their lives)*

While devices were initially designed and approved for use as a bridge strategy, newer-generation LVADs have been implanted in patients with contraindications to transplantation and with little likelihood for recovery. This newer "destination therapy" indication has translated into more and more patients being eligible for mechanical assist support. While only 2% of LVAD implants worldwide were categorized as "destination therapy" in 2009, this proportion had increased dramatically to 49% in 2017 according to the 2019 annual report from the Society of Thoracic Surgeons (STS) Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database which captures peri-operative and long-term data on LVAD patients at participating institutions worldwide and publishes annual reports highlighting utilization trends and outcomes data[3]. The increased numbers of patients on LVAD support for destination therapy has also led to patients being on support for extended periods of time and has given us an opportunity to study the long-term physiologic changes which can be seen while on LVAD support. Despite the above categorical initial implantation intents, patients often have clinical events or changes in goals of care which may change the device support strategy.

2.3.2.3 Side Effects of LVAD

Like any surgically implantable device, LVADs do carry an inherent risk profile which must be weighed against its purported benefits. Since LVAD implantation introduces a

foreign material to the patient's circulation, LVAD recipients must be anticoagulated following device insertion and frequently have either bleeding or thrombotic complications. Additionally, given that the driveline which supplies power and relays commands to the pump must be tunneled through the skin, this creates a permanent tract for skin-borne pathogens to enter the body, hence making driveline-related infections the other common complication associated with LVADs. According to the STS-INTERMACS database, the latest generation of centrifugal pump LVADs have a reported incidence of 28% for pump-related infections, 20% for gastrointestinal bleeding, and 20% for strokes or transient ischemic attacks at one year[3]. These figures are similar to those published by four Canadian heart failure centers who reported a gastrointestinal bleeding rate of 15% and ischemic stroke rate of 21% at one year following HVAD (HeartWare continuous-flow Ventricular Assist Device) centrifugal pump device insertion[24].

2.3.2.4 Trends in LVAD Utilization

Advances in LVAD technology and the increased familiarity with LVADs as a whole has resulted in a rapid growth in the number of LVADs implanted worldwide and across Canada. In 2019, the STS-INTERMACS reported that the number of continuous-flow LVADs implanted worldwide (at participating institutions) increased from approximately 400 in 2008 to over 2000 in 2017[3]. A study which examined LVAD implantation rates in Medicare beneficiaries (perhaps more representative of the general population than the STS-INTERMACS membership) also reported increasing rates of device implantation. This study by Lampropulos et al. calculated LVAD implantation rates of 3.7 per 1,000,000

person years in 2004 vs. 21.9 per 1,000,000 person-years in 2011[25], mirroring the increase seen in the STS-INTERMACS registry.

Parallel to this trend had been an increase in the proportion of heart transplant candidates being bridged to transplantation with mechanical circulatory support. The International Society for Heart and Lung Transplantation (ISHLT) reported in 2018 that the proportion of heart transplant recipients being bridged to transplantation with LVAD support more than doubled from 2006 (23%) to 2016 (54%)[26].

2.3.3 Cost Comparison of Orthotopic Heart Transplantation and LVAD

Given the relatively high costs associated with LVADs and their large potential patient target population, there have been numerous studies examining the financial feasibility and cost effectiveness of these devices.

An American comparative study for survival and cost of heart transplantation and LVAD published in 2013 looked at all patients having undergone either treatment modality in the United States from 2005 to 2009. The authors reported that during that time period, while the rates of transplantation remained relatively stable (1744 to 2227 patient annually), LVAD implantation rates nearly tripled (811 to 2298). In-hospital mortality for transplantation ranged from 3.8% to 6.5% while LVAD mortality during the index hospitalization decreased significantly from 42.3% to 17.0% over the same time period as new and better devices were brought onto the market. In this same study, the average cost

per patient for the index hospitalization increased from $120,413 USD to $168,576 USD for those receiving a transplant and from $177,508 USD to $208,522 USD in the LVAD cohort[27]. Therefore, despite carrying a worse prognosis, LVAD implantation is significantly more expensive than orthotopic heart transplantation, but LVAD implantation rates continue to increase due to the rising prevalence of heart failure, limited organ donor supply, and changing criteria for device implantation.

A Canadian economic analysis attempted to quantify the costs associated with LVAD therapy in patients are ineligible for transplantation, and hence qualified as "bridge to transplant". The authors concluded that, in a cohort of patients with end-stage heart failure deemed ineligible for transplantation, the cost of continuous-flow LVADs was much higher ($284,000) compared to medical management ($32,000) over a lifetime horizon but had higher quality-adjusted life-years (1.48 vs. 0.39). This resulted in an incremental cost per quality-adjusted life year gained of $231,000[28]. A report from the *Institut national d'excellence en santé et en services sociaux du Québec* similarly concluded that, despite remarkable clinical and survival benefits, LVAD use in advanced heart failure was not cost effective but yet recommended a structured and controlled implementation of the technology in this patient demographic[29].

2.3.4 Pulmonary Hypertension Reversibility in LVAD

In the early days of LVAD implementation, patients were carefully selected for device support and were mostly considered as candidates for bridge to transplantation. As such, most patients who had a contraindication to transplantation were not considered candidates

for LVAD support. It was for this reason that very few patients with pulmonary hypertension had an LVAD inserted. Despite this, there were a few case reports and case series reported in the early 2000s which demonstrated reversibility of what was initially thought to be fixed pulmonary hypertension while on LVAD. One of the largest of such series was published in 2007 by a group in Vienna, Austria. In this series, they reported the outcomes of 35 consecutive patients with end-stage heart failure and what was believed to be fixed pulmonary hypertension (which they defined as a PVR > 3 Wood units). Despite these patients being supported by early-generation LVAD pumps, they reported observing a reduction in the mean PVR of patients from 5.1 ± 2.8 Wood units pre-operatively to 2.0 ± 0.8 at 6-week follow-up[30]. This observed reversibility of pulmonary hypertension then led to transplantation candidacy, and 24/35 patients had successful bridging to transplantation with the remaining 11 patients dying while on device support. Importantly, of those who were transplanted, survival at one-year post-transplant was 95% which suggests that the normalization of pulmonary pressures while on device support is a change which may persist throughout device explant and eventual transplantation. What is not known is whether patients with more severe or longstanding pulmonary hypertension may have irreversible disease which would not respond to left ventricular off-loading with mechanical circulatory support devices or if their response would be tempered in amplitude or duration.

A Canadian group published their series of LVAD implants as bridge to transplantation or candidacy. In the series of 37 patients from 2001 to 2009, 59% were not deemed transplant candidates at the time of LVAD insertion, the majority having pulmonary hypertension as

a contraindication. 73% of patients who were initially deemed transplant-ineligible were eventually listed and underwent heart transplantation but a comparative analysis to their normotensive cohort revealed lower one-year survival amongst those bridged to transplantation candidacy (67% vs 100%, p=0.05)[31].

2.3.5 Pulmonary Hemodynamics

2.3.5.1 Right Heart Catheterization

Right heart catheterization is required to make a definitive diagnosis of pulmonary hypertension. In addition to providing direct measurements of pulmonary pressures, right heart catheterization allows for the simultaneous measurement of cardiac output (as determined by thermodilution or Fick measured oxygen consumption) and the calculation of pulmonary vascular resistance[32].

In right heart catheterization, a thin catheter is inserted through a venous puncture (typically the jugular or femoral vein) and advanced through the right heart and into the pulmonary circulation. The catheter is then connected to a pressure transducer and measurements are taken at various levels (right atrium, pulmonary artery, pulmonary capillary wedge) which permit the calculation of various pulmonary hemodynamic parameters. At time of catheterization, pharmacological adjuncts can be used to determine pulmonary vasoreactivity such as inhaled nitric oxide or intravenous epoprostenol. Criteria for the assessment of pulmonary vasoreactivity have been proposed and may be used to guide management strategies[33].

Despite the invasive nature of right heart catherization, the safety of the procedure in patients with pulmonary hypertension has been well established. In a study of 7,218 right heart catheterization performed at experienced centers, the overall rate of serious adverse events was reported at 1.1% (95% confidence interval 0.8%-1.3%). Venous access-related complications such as hematoma formation or pneumothorax, or lung collapse, occurred most frequently followed by arrhythmias. Peri-procedural mortality was exceedingly rare (procedure-related mortality of 0.055%, 95% confidence interval 0.001% to 0.099%)[34].

2.3.5.2 Echocardiography

Although right heart catheterization remains the gold standard in the measurement of pulmonary arterial pressures and hence in the diagnosis and monitoring of pulmonary hypertension, echocardiography also provides estimates which may be useful for the screening of pulmonary hypertension in patients with cardiac disease. In patients with any degree of tricuspid valve regurgitation (common in heart failure), transthoracic echocardiography may be used to estimate right ventricular systolic pressure by adding the velocity of the tricuspid regurgitation jet to a given right atrial pressure. In the absence of pulmonary valve stenosis, right ventricular systolic pressure may then be used as a surrogate for pulmonary artery systolic pressure[35].

Transthoracic echocardiography is far more accessible and less invasive than right heart catheterization. However, its utility as an alternative to right heart catheterization in the diagnosis and monitoring of pulmonary hypertension in our LVAD population was brought

into doubt by a recent systematic review and meta-analysis of 29 studies that found that sensitivity and specificity for echocardiography in diagnosing pulmonary hypertension was only 83% (95% CI 73 to 90) and 72% (95% CI 53 to 85; n=12), respectively. The same study found that the correlation coefficient between systolic pulmonary arterial pressure estimated from echocardiography and that measured by right heart catheterization was just 0.70 (95% CI 0.67 to 0.73; n=27)[36].

3 Objectives

The objectives of the study were as follows:

1. To characterize the LVAD experience at the Maritime Heart Center (Halifax, NS) and the Brigham and Women's Hospital (Boston, MA) by capturing and summarizing patient characteristics and outcomes following LVAD insertion
2. To quantify the changes in pulmonary hypertension over time observed in patients following LVAD insertion and to determine if any pre-operative variables have a significant effect on post-operative pulmonary hemodynamics
3. To determine if the pulmonary hypertension reversibility experienced while on mechanical assist support persists following heart transplantation

4 Methods

4.1 Patient Selection

4.1.1 Participating Institutions

This study is a collaborative project between the Divisions of Cardiac Surgery at the Maritime Heart Center (Halifax, NS) and the Brigham and Women's Hospital (Boston, MA). Both centers have long-standing comprehensive heart failure programs which include surgical management through mechanical assist devices and transplantation. Research Ethics Board approval was obtained from both institutions for data acquisition and analysis.

4.1.2 Inclusion Criteria

Patients who had a durable LVAD inserted for end-stage heart failure during the study period (January 1, 2009 to January 1, 2019) were considered for inclusion. Once patients had been identified and their pulmonary hemodynamic measurements captured, our study population was further refined to those with both pre-operative (within 90 days of LVAD implantation) and post-operative right heart catheterization data available for measurement and analysis.

4.1.3 Exclusion Criteria

Patients were excluded if they had undergone insertion of a right ventricular assist device (RVAD) or had documented pre-existing lung pathology which may negatively affect the

pulmonary vasculature and prevent normalization of pulmonary pressures despite left ventricular offloading from LVAD support.

4.2 Pulmonary Hemodynamic Monitoring

Serial hemodynamic measurements were retrieved from institutional electronic medical records for 90 days prior to LVAD insertion and up to the patient's death or loss to follow-up in order to capture temporal trends in pulmonary hemodynamic measurements. Pulmonary hemodynamic parameters captured included date of catheterization, cardiac output (CO), central venous pressure (CVP), mean pulmonary artery pressure (mPA) and pulmonary capillary wedge pressure (PCWP). These parameters then allowed for calculation of the transpulmonary gradient (TPG) in mmHg as well as pulmonary vascular resistance (PVR) in Wood Units as follows:

$$TPG = PA_{mean} - PCWP$$

$$PVR = \frac{TPG}{CO} = \frac{PA_{mean} - PCWP}{CO}$$

The date of right heart catheterization and day of LVAD insertion were used to calculate a "catheterization interval" and day 0 was defined as the day of LVAD insertion. A secondary analysis was also undertaken to examine the effect of pre-LVAD pulmonary hypertension on pulmonary pressures following transplantation for those patients who were

successfully bridged to transplantation while on device support. For the purposes of this secondary analysis, day 0 was defined as the day of transplantation.

4.3 Covariates

Once patients had been identified, demographics and other preoperative variables were recovered from the perioperative databases of both institutions. In Halifax, the Maritime Heart Center Registry is a prospective database established in 1993 which includes all patients having undergone cardiac surgery at this institution and captures peri-operative characteristics as well as 30-day in-hospital outcomes. In Boston, Partners Healthcare Research Patient Data Registry is a comprehensive, centralized clinical data registry contains data on ~10 million patients from all institutions within the Partners HealthCare System. Both databases are regularly audited and have been utilized for numerous observational studies.

The data retrieved from these electronic records included the type of cardiomyopathy (ischemic or non-ischemic), ejection fraction, cardiac risk factors (hypertension, dyslipidemia, smoking, diabetes), chronic kidney disease, and COPD. These variables were selected for analysis as they have all been previously reported to portend prognostic significance for survival following LVAD implantation in the STS-INTERMACS registry[3].

Operative details captured included date of implantation, type of device, cardiopulmonary bypass time and aortic crossclamp time.

Post-operative outcomes of interest included whether the patient recovered to device explantation, date of explantation (if applicable), whether the patient progressed to heart transplantation, date of transplantation (if applicable), in addition to the pulmonary hemodynamic parameters mentioned previously. The data which were not available through the prospective institutional databases were retrospectively retrieved from each patient's electronic medical records at their respective institution whenever possible.

4.4 Statistical Analysis

Following the merger of both databases and the anonymization of each patient's identifying information, we began by generating summary statistics of the study population. Descriptive characteristics of our patient population were generated, and outcomes were presence of absence of pre-LVAD pulmonary hypertension (defined as calculate PVR > 3 Wood Units) and implanting center. Continuous variables were compared using a two-tailed t-test or Wilcoxon rank sum test, and categorical variables were analyzed by chi-square or Fisher's exact test, as appropriate.

In order to generate visual representations of our pulmonary hemodynamic data over the study period, longitudinal measurements were graphed by patient identifier for each metric (mPA, PCWP, cardiac output, and PVR) and stratified by whether or not the patient had calculated pulmonary hypertension prior to their LVAD implant. For visualization purposes, a line of best fit was added to these graphs with the "qfitci" function from Stata

which plots the prediction based on a quadratic regression and adds a 95% confidence interval.

Given the nature of our longitudinal data (related observations based on individual patients and observations spaced unevenly in time), generalized estimating equation models[37] were generated to examine the association of post-operative changes in longitudinal pulmonary vascular resistance calculations with pre-operative pulmonary hypertension status and other variables of interest (such as type of LVAD, implanting institution, age, and ejection fraction). In the case of binary cardiac risk variables, the absence of the risk factor was used as referent for regression and in the case of categorical variables, the category with the lowest expected risk was used as referent.

To better model clinical decision making, normalization of PVR by 3 and 6 months post LVAD implantation was used to create a binary outcome, which was analyzed through multiple logistic regression on the peri-operative variables mentioned above. We chose to examine PVR status at 3, 6, and 12 months for our study patients as these timelines are often referred to in the ISHLT guidelines[38]. If patients had a calculated PVR of less than 3 Wood Units at any time point prior to each date, they were then considered to have normalized their pulmonary pressures (even if they were to have subsequent increase in PVR to above 3 Wood Units). They were still categorized as having pulmonary hypertension if their pulmonary pressures did not drop below the 3 Wood Units threshold or if they had died before normal pressures were measured by right heart catheterization.

Given the differences in healthcare structure and policies between the two study institutions, the implanting institution was included as a covariate in our regression modeling. All analyses were performed with PVR either as a continuous or categorical variable to determine whether the magnitude or severity of pulmonary hypertension had a variable effect based on reversibility.

A secondary analysis was undertaken in those who had survived to transplantation in order to determine whether pre-LVAD pulmonary hypertension was associated with post-transplantation changes in pulmonary hemodynamics and early right ventricular failure and death or if the reversibility achieved while on device support persisted following transplantation.

An alpha value of 0.05 was used for statistical significance. All statistical analyses were performed with Stata 15.1 (StataCorp, College Station, Tx).

5 Results

5.1 Summary Statistics

Our retrospective analysis revealed that a total of 177 patients had an LVAD implanted at one of the two institutions during the study period and met our inclusion and exclusion criteria. 25 patients were excluded as they did not have at least one pre-operative (within 90 days of LVAD implantation) and one post-operative right-heart catheterization. Once the peri-operative data had been retrieved for all patients, summary statistics were generated.

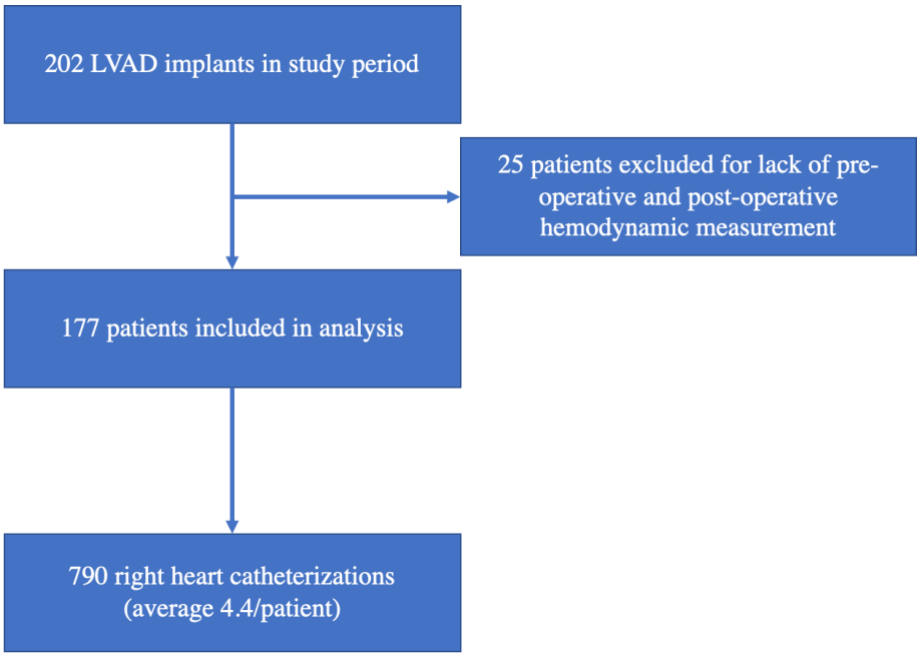

Figure 2: Patient flow diagram

5.1.1 Patient Demographics by Pre-Operative Pulmonary Hypertension Status

Table 1 summarizes the demographic information for all patients stratified by presence or absence of significant pre-operative pulmonary hypertension, as defined by a calculated pre-operative PVR greater than or equal to 3 Wood Units. Of the 177 patients, 107 (60.5%) had pulmonary hypertension by pre-operative right heart catheterization. The two groups' patient characteristics were well balanced with a few notable exceptions. Patients with pulmonary hypertension were more likely to have had their LVAD implanted at Brigham and Women's Hospital than those without pre-operative pulmonary hypertension (84% vs. 71%, p=0.04). Additionally, patients with elevated pre-operative PVR were more likely to have had a non-ischemic cardiomyopathy (as compared to ischemic) for primary etiology (69% vs. 51%, p=0.01).

Otherwise, the two groups stratified by pre-operative pulmonary hypertension status were similar. The average age at time of implantation was 53 years, 79% of those included were male, and the average ejection fraction was 18%. 39 patients (23%) had prior cardiac surgery and as such underwent redo-sternotomy with their LVAD implant. There were five types of LVAD implanted over the study period and these were (in order of decreasing frequency): HeartMate II (59%), HeartWare HVAD (21%), HeartMate III (16%), HeartMate XVE (2%), and Thoratec PVAD (2%). One hundred and seven (60%) patients were successfully bridged on device support to transplantation (mean time between LVAD implantation and transplantation 461 ± 413 days) and only 2 patients (1.1%) had their LVAD explanted for recovery.

	PVR < 3 WU N=70	**PVR ≥ 3WU** N=107	**Total** N=177	**p-value**
Age	53 (12)	52 (13)	53 (13)	0.55
Sex				0.97
Male	55 (79%)	84 (79%)	139 (79%)	
Female	12 (17%)	18 (17%)	30 (17%)	
Implanting Center				**0.04**
Boston	50 (71%)	90 (84%)	140 (79%)	
Halifax	20 (29%)	17 (16%)	37 (21%)	
Smoking History	32 (48%)	50 (49%)	82 (49%)	0.87
Hypertension	30 (45%)	53 (52%)	83 (49%)	0.36
Diabetes	22 (33%)	38 (37%)	60 (36%)	0.56
Dyslipidemia	45 (67%)	75 (74%)	120 (71%)	0.37
Chronic Obstructive Pulmonary Disease	6 (15%)	4 (12%)	10 (14%)	0.65
Cardiomyopathy				**0.01**
Ischemic	31 (44%)	28 (26%)	59 (33%)	
Non-Ischemic	36 (51%)	74 (69%)	110 (62%)	
Missing	3 (4%)	5 (5%)	8 (5%)	
Chronic Kidney Disease	13 (42%)	17 (40%)	30 (41%)	0.90
Ejection Fraction (%)	18 (6)	18 (6)	18 (6)	0.90
Prior Cardiac Surgery	13 (19%)	26 (25%)	39 (23%)	0.36
Clamp Time (minutes)	22 (32)	26 (22)	24 (27)	0.64
Cardiopulmonary Bypass Time (minutes)	115 (72)	116 (55)	115 (62)	0.90
LVAD Type				0.22
HM2	44 (63%)	60 (56%)	104 (59%)	
HM3	13 (19%)	16 (15%)	29 (16%)	
HVAD	11 (16%)	26 (24%)	37 (21%)	
PVAD	0 (0%)	4 (4%)	4 (2%)	
XVE	2 (3%)	1 (1%)	3 (2%)	
Transplanted	47 (67%)	60 (56%)	107 (60%)	0.14
Device Explanted	0 (0%)	2 (2%)	2 (1%)	0.29

Table 1: Patient demographics by pre-operative pulmonary hypertension status.

5.1.2 Patient Demographics by Implanting Center

In order to further delineate the patient characteristics from both study institutions and how they might differ from each other, demographic statistics were also generated and stratified

according to implanting center. As can be seen from Table 2 below, patient characteristics were markedly different between Halifax and Boston on numerous fronts, as could likely have been expected given the different health policies, practices, and referral patterns between the Canadian and American healthcare systems.

During the study's inclusion period, 140 patients from Boston and 37 patients from Halifax met our eligibility criteria, representing 79% and 21% of our study population. Notably, patients who had their LVADs implanted in Boston were more likely to have pre-operative pulmonary hypertension (64% compared to 46%, $p=0.04$), to have dyslipidemia (75% compared to 52%, $p=0.01$), and to have a diagnosis of chronic obstructive pulmonary disease (20% compared to 3%, $p=0.04$). The average ejection fraction was slightly higher for Boston patients compared to their Halifax counterparts ($19 \pm 6\%$ compared to $14 \pm 7\%$, $p<0.01$) and the distribution of VAD models was skewed towards the newer-generation HeartMate III in Boston. Finally, a significantly larger proportion of Halifax patients progressed to heart transplantation while on LVAD support compared to Boston (86% compared to 54%, $p<0.01$).

	Boston N=140	**Halifax** N=37	**Total** N=177	**p-value**
Age (Years)	53 (13)	51 (13)	53 (13)	0.40
Sex				0.94
Male	115 (82%)	24 (65%)	139 (79%)	
Female	25 (18%)	5 (14%)	30 (17%)	
Pre-Operative Pulmonary Hypertension	90 (64%)	17 (46%)	107 (60%)	**0.04**
Smoking History	67 (48%)	15 (52%)	82 (49%)	0.70
Hypertension	73 (52%)	10 (34%)	83 (49%)	0.08
Diabetes	53 (38%)	7 (24%)	60 (36%)	0.16
Dyslipidemia	105 (75%)	15 (52%)	120 (71%)	**0.01**
Chronic Obstructive Pulmonary Disease	9 (20%)	1 (3%)	10 (14%)	**0.04**
Cardiomyopathy				0.42
Ischemic	47 (34%)	12 (32%)	59 (33%)	
Non-Ischemic	93 (66%)	17 (46%)	110 (62%)	
Missing	0 (0%)	8 (22%)	8 (5%)	
Chronic Kidney Disease	19 (43%)	11 (38%)	30 (41%)	0.66
Ejection Fraction (%)	19 (6)	14 (7)	18 (6)	**<0.01**
Prior Cardiac Surgery	35 (25%)	4 (14%)	39 (23%)	0.19
Clamp Time (minutes)	38 (19)	10 (27)	24 (27)	**<0.01**
Cardiopulmonary Bypass Time (minutes)	114 (62)	123 (63)	115 (62)	0.48
LVAD Type				**0.01**
HM2	79 (56%)	25 (68%)	104 (59%)	
HM3	29 (21%)	0 (0%)	29 (16%)	
HVAD	25 (18%)	12 (32%)	37 (21%)	
PVAD	4 (3%)	0 (0%)	4 (2%)	
XVE	3 (2%)	0 (0%)	3 (2%)	
Transplanted	75 (54%)	32 (86%)	107 (60%)	**<0.01**
Device Explanted	2 (1%)		2 (1%)	

Table 2: Patient demographics by implanting center.

5.2 Right Heart Catheterization Data

Following electronic chart reviews and data abstraction, data on a total of 790 right heart catheterizations were included in our analysis. The mean number of captured observations (or right heart catheterization instances) per patient was 4.4.

Figure 2 represents a visual depiction of longitudinal measurements of the mean pulmonary artery (mPA) pressures for patients with and without pre-operative pulmonary hypertension. While the y-axis depicts the mPA pressure in mmHg, the x-axis represents the days since the index LVAD implantation for each patient.

As expected, the initial mPA of patients with pre-operative pulmonary hypertension as defined as a calculated PVR $\geq$ 3 Wood Units was higher than their normotensive counterparts and it appears that both groups typically had lowering of their pulmonary pressures over time while on device support.

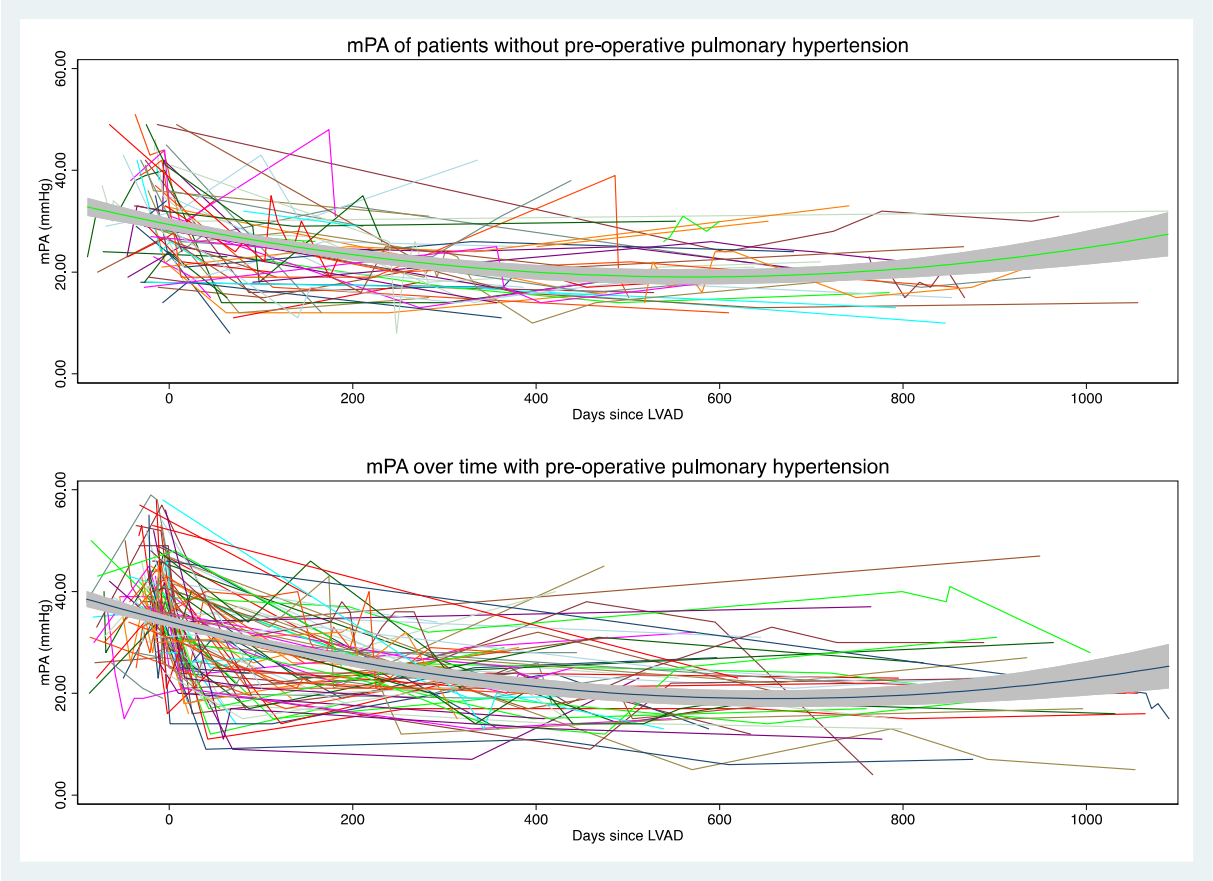

Figure 3: Mean pulmonary artery (mPA) pressure over time.

Also obtained from serial right heart catheterization data, longitudinal pulmonary capillary wedge pressures are charted in Figure 3 below. Similar to the mPA pressures mentioned above, left atrial pressures appeared to decrease following LVAD implantation and left ventricular offloading with device support for patients both with and without pre-operative pulmonary hypertension. This effect appears to be most pronounced in the first few months after LVAD implant but continues well into their first year on device therapy. Unlike mPA

measurements, both cohorts appeared to start at a similar mean wedge pressure, likely reflecting similar levels of left ventricular dysfunction at time of implant.

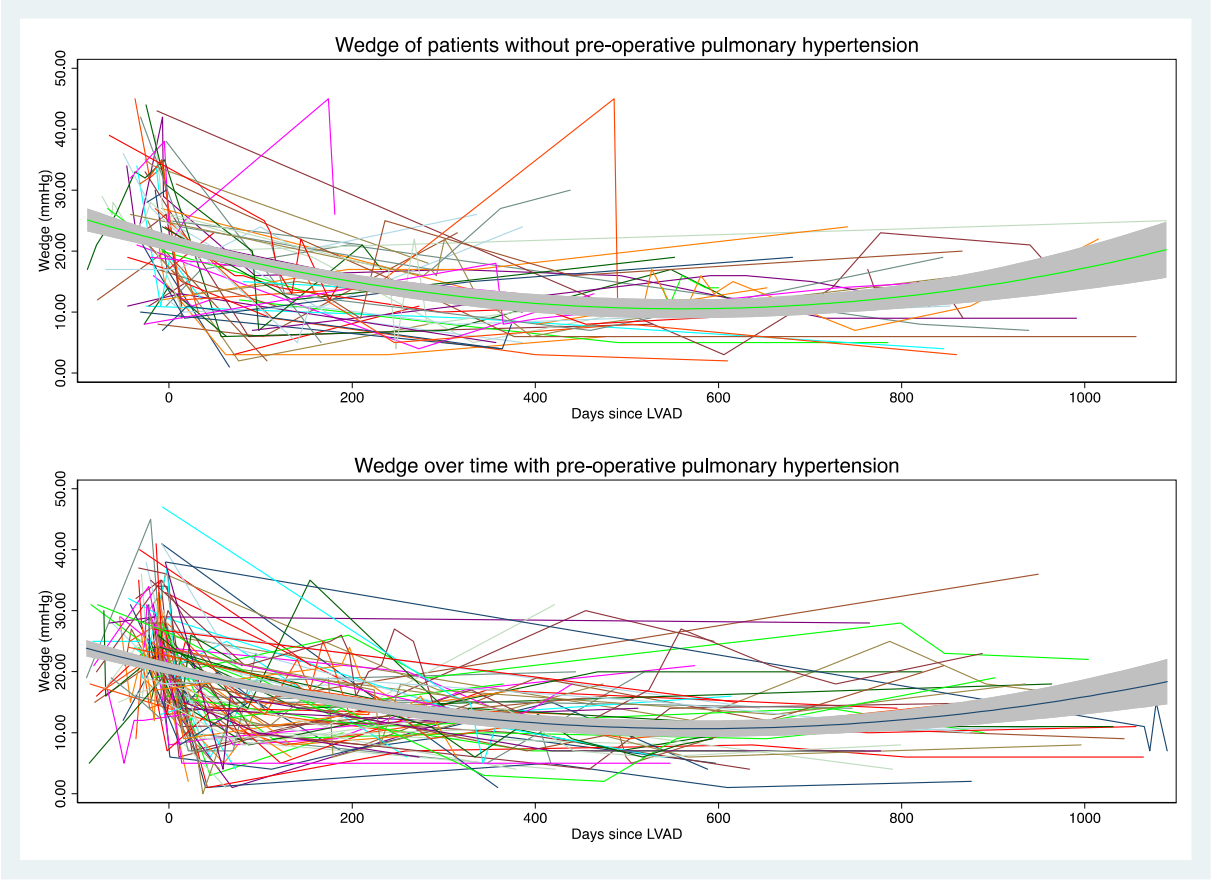

Figure 4: Pulmonary capillary wedge pressure over time.

Figure 4 charts the measured cardiac output as captured through right heart catheterization. As expected from a device which augments the heart's native cardiac output, serial cardiac output measurements appeared to increase over time for patients with and without pre-operative pulmonary hypertension.

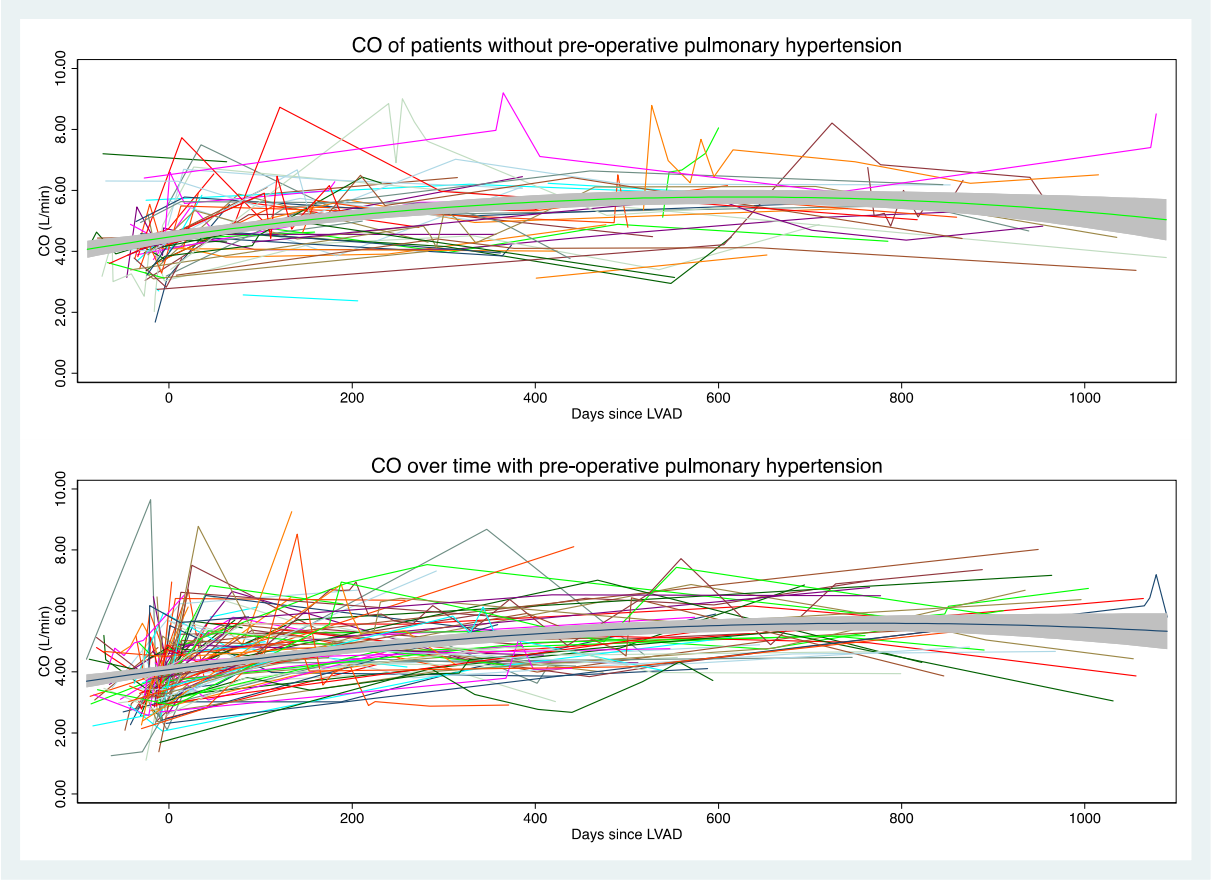

Figure 5: Cardiac output over time.

The calculated PVR values for every right heart catheterization are charted below in Figure 5 and have been stratified according to pre-operative pulmonary hypertension. Although longitudinal PVR measurements appear to remain relatively constant for patients without pre-operative pulmonary hypertension, there is a clear decrease in calculated PVR over time for those with pre-operative pulmonary hypertension and this effect appears most pronounced for the first few months on device support.

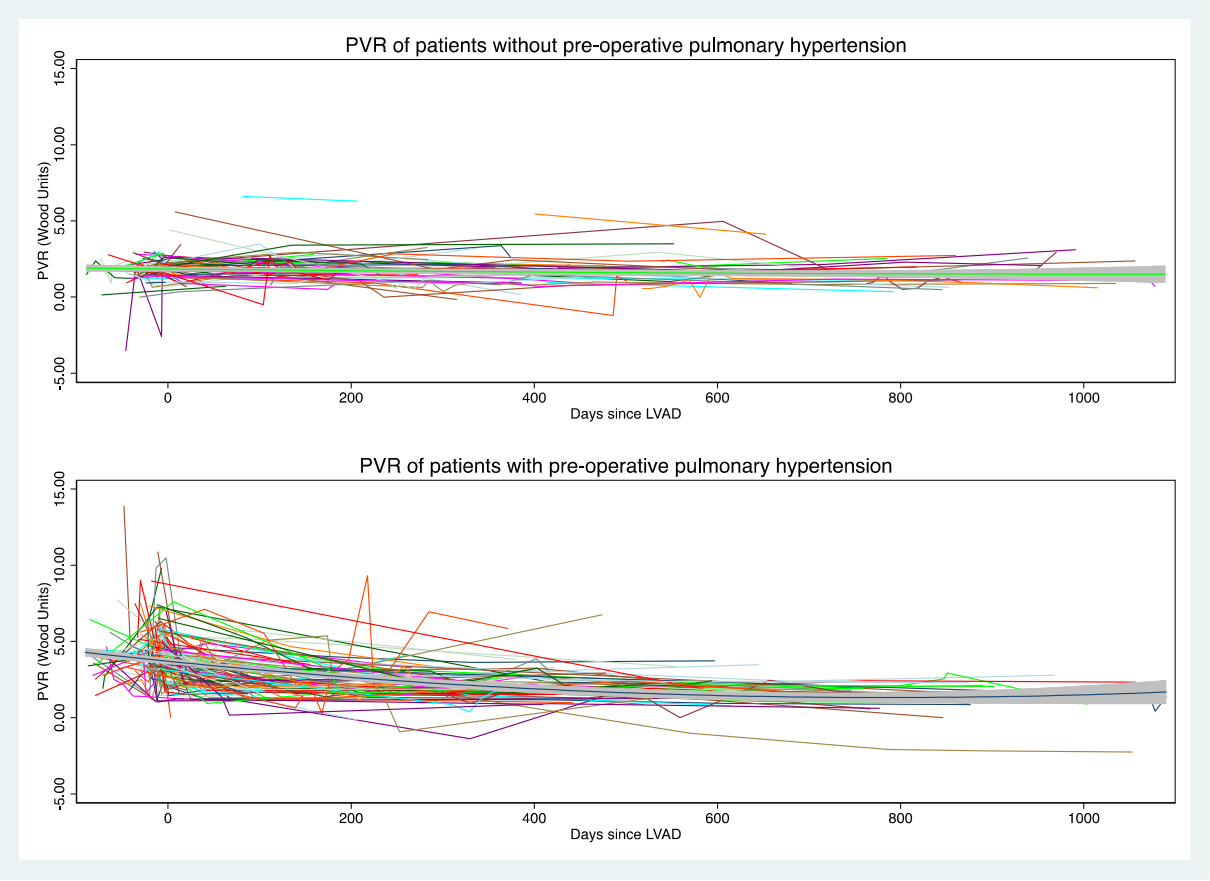

Figure 6: Calculated PVR over time

In order to further quantify the pulmonary hypertension reversibility experience while on LVAD support, we also captured whether patients had normalized their PVR at different timepoints. As can be seen in Table 3 below, more than 60% of included patients had pulmonary hypertension at time of implant and this proportion was reduced by nearly half at the 3-month mark. There was continued regression in the following 3 months as the

proportion of patients with pulmonary hypertension decreased from 31.6% to 23.2% at 6 months and an even further reduction to 14.1% at 12 months post LVAD implant.

	Pre-Operative	**3 months**	**6 months**	**12 months**
PVR ≥ 3 WU	107 (60.5%)	56 (31.6%)	41 (23.2%)	25 (14.1%)
PVR < 3 WU	70 (39.5%)	121(68.4%)	136 (76.8%)	152 (85.9%)

Table 3: PVR Status at 3, 6, and 12 months.

For the purposes of exploratory analysis, patients who were subsequently transplanted were also followed post-transplant and their right heart catheterization measurements captured until time of loss to follow-up or death. Their post-transplant PVR measurements were calculated and are displayed in Figure 6. Once again, patients are stratified according to their pre-LVAD pulmonary hypertension status. This data seems to indicate that the reversibility of pulmonary hypertension experienced while on LVAD support persists following orthotopic heart transplantation. This observation has important clinical implications as elevated pulmonary pressures following transplantation can lead to right ventricular failure and eventual death. With one notable exception, our data seems to indicate that patients who were identified as having pre-LVAD pulmonary hypertension followed by normalization of pulmonary pressure on LVAD support maintained normal PVR following device removal and transplantation.

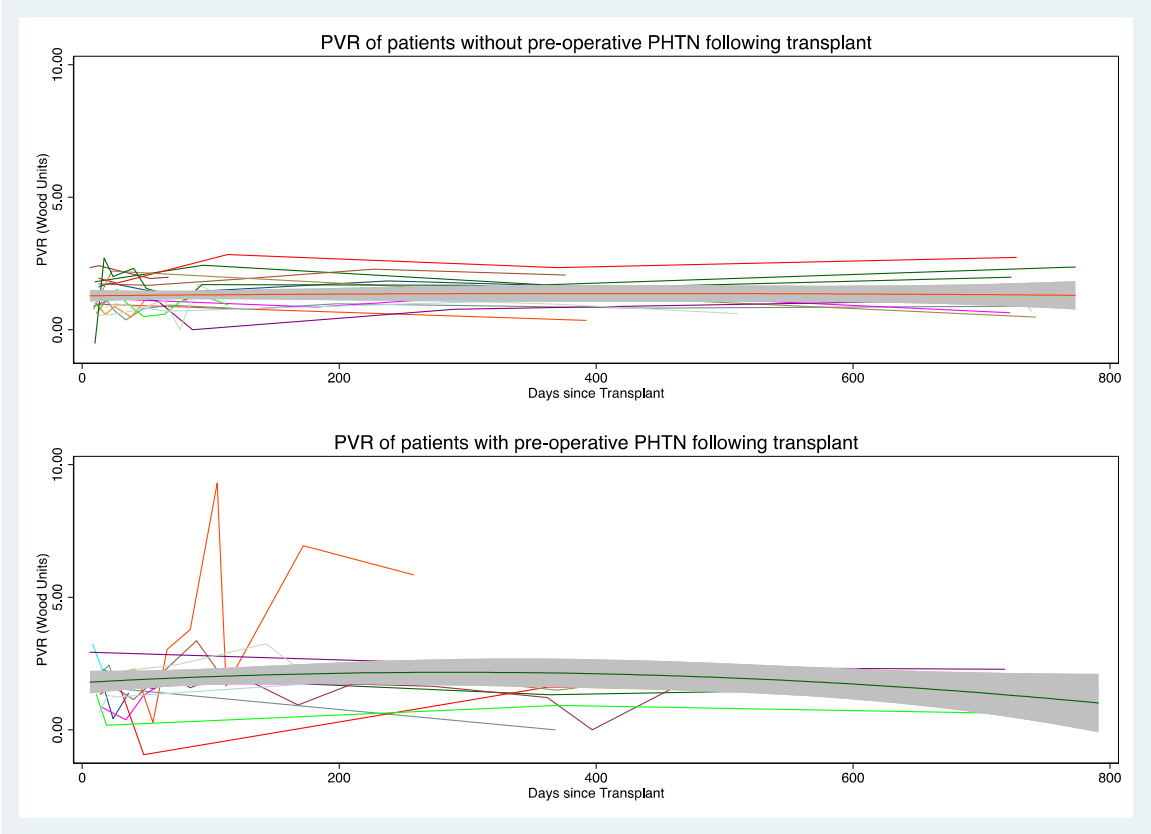

Figure 7: Calculated PVR of patients following cardiac transplantation

5.3 Generalized Estimating Equations

In order to assess the marginal effect of our pre-operative variables on post-LVAD pulmonary pressures, generalized estimating equations (GEE) with independent correlation structure were calculated for our panel data. Table 4 summarizes the GEE for PVR based on a number of peri-operative variables. Variables that were found to have a significant effect on post-implant pulmonary hypertension were pre-operative PVR and the implanting center. Other cardiac risk factors such as smoking, hypertension, diabetes, and

dyslipidemia did not appear to have a significant effect nor did the age of the patient, whether they had prior cardiac surgery, the type of cardiomyopathy responsible for the patient's clinical status, their ejection fraction, or the type of LVAD implanted.

	Coefficient	**[95% Conf. Interval]**		**p-value**
Pre-Operative PVR	0.37	0.30	0.44	**<0.01**
Implanting Center				
Boston	*Referent*			
Halifax	-0.53	-0.87	-0.19	**<0.01**
Sex				
Male	*Referent*			
Female	0.15	-0.25	0.56	0.46
Age	0.01	0.00	0.03	0.06
Smoking	0.18	-0.08	0.43	0.18
Hypertension	-0.23	-0.48	0.02	0.07
Diabetes	0.14	-0.13	0.40	0.32
Dyslipidemia	0.23	-0.05	0.51	0.11
Cardiomyopathy				
Ischemic	*Referent*			
Non-Ischemic	0.22	-0.06	0.50	0.12
Ejection Fraction	0.00	-0.02	0.02	0.77
Prior Cardiac Surgery	0.23	-0.23	0.68	0.33
VAD				
HM2	*Referent*			
HM3	-0.15	-0.50	0.20	0.41
HVAD	-0.05	-0.40	0.30	0.76
PVAD	-0.29	-0.63	0.05	0.09
XVE	-0.62	-1.45	0.20	0.14

Table 4: Generalized estimating equation regression with pre-operative PVR as continuous variable.

In an attempt to further delineate the effect of pre-operative PVR value (or the magnitude of calculated pulmonary hypertension) on post-implant changes in pulmonary pressures, a categorical variable was generated for PVR with cutoff values of 3, 5, 7, and 9 Wood Units.

Generalized Estimating Equations were again calculated on the same data and all categories of pre-operative PVR appeared to have a significant effect on post-implant pulmonary pressures. Higher values of pre-operative PVR appeared to have proportional effect size on subsequent PVR measurements with increasing coefficient values as can be seen in Table 5 below. Once again, pre-LVAD pulmonary vascular resistance values and implanting center had a significant effect on subsequent changes in pulmonary vascular resistance.

	Coefficient	[95% Conf. Interval]		p-value
Pre-Operative PVR				
<3	*Referent*			
3 to 5	0.88	0.62	1.13	**<0.01**
5 to 7	1.73	1.23	2.23	**<0.01**
7 to 9	2.11	1.40	2.81	**<0.01**
>9	3.80	2.07	5.53	**<0.01**
Center				
Boston	*Referent*			
Halifax	-0.56	-0.91	-0.22	**<0.01**
Sex				
Male	*Referent*			
Female	0.12	-0.27	0.51	0.54
Age	0.01	0.00	0.03	0.09
Smoking	0.19	-0.08	0.45	0.17
Hypertension	-0.25	-0.49	0.00	0.05
Diabetes	0.25	-0.01	0.52	0.06
Dyslipidemia	0.23	-0.06	0.51	0.12
Cardiomyopathy				
Ischemic	*Referent*			
Non-Ischemic	0.20	-0.11	0.51	0.21
Ejection Fraction	0.00	-0.02	0.03	0.77
Prior Cardiac Surgery	0.19	-0.26	0.64	0.41
VAD Type				
HM2	*Referent*			
HM3	-0.12	-0.51	0.26	0.53
HVAD	-0.08	-0.43	0.26	0.63
PVAD	-0.36	-0.85	0.13	0.15
XVE	-0.87	-1.88	0.13	0.09

Table 5: Generalized estimating equation regression with pre-operative PVR as a categorical variable.

5.4 Logistic Regression

In an effort to determine whether pre-operative variables would have an effect on PVR status at pre-specified time-points, new variables were generated according to PVR status at 3 and 6 months, as mentioned previously. We then performed logistic regression of these

variables with pre-operative PVR as either a continuous or categorical variable at the cutoff values noted above.

Table 6 summarizes the logistic regression with PVR at 3 and 6 months as the outcome of interest and using pre-operative PVR as a continuous variable. In this regression, pre-operative PVR, implanting center, and the HeartMate III LVAD were all found to have a significant effect on the pulmonary hypertension status at 3 months post LVAD implant. Variables that are omitted predicted failure perfectly in our model (given their small sample size) and so automatically excluded from the analysis by the statistical software.

At 6 months, pre-operative PVR was the only variable that was found to have a significant effect on pulmonary hypertension status. Again, given the relatively small sample size and high rate of reversibility, most of the LVAD models actually predicted model failure perfectly and so are omitted from the results.

	3 Month Analysis				6 Month Analysis			
	Odds Ratio	**[95% Conf. Interval]**		**p-value**	**Odds Ratio**	**[95% Conf. Interval]**		**P>z**
Pre-Operative PVR	1.50	1.20	1.89	**<0.01**	1.34	1.08	1.66	**0.01**
Implanting Center								
Boston	*Referent*				*Referent*			
Halifax	6.00	2.00	17.98	**<0.01**	1.90	0.61	5.92	0.27
Sex								
Male	*Referent*				*Referent*			
Female	0.98	0.31	3.13	0.98	1.76	0.54	5.77	0.35
Age	1.04	1.00	1.08	0.07	1.03	0.98	1.07	0.25
Smoking	1.26	0.52	3.06	0.61	1.68	0.65	4.32	0.28
Hypertension	0.62	0.24	1.60	0.32	1.33	0.48	3.66	0.59
Diabetes	1.50	0.59	3.81	0.39	1.44	0.53	3.91	0.47
Dyslipidemia	0.82	0.25	2.73	0.75	0.70	0.19	2.59	0.60
Cardiomyopathy								
Ischemic	*Referent*				*Referent*			
Non-Ischemic	0.67	0.24	1.86	0.45	0.59	0.20	1.75	0.34
Ejection Fraction	1.00	0.93	1.07	0.95	0.93	0.86	1.01	0.08
Prior Cardiac Surgery	1.49	0.54	4.13	0.44	2.02	0.68	5.98	0.20
VAD								
HM2	*Referent*				*Referent*			
HM3	0.07	0.01	0.59	**0.02**	*Omitted*			
HVAD	0.73	0.25	2.15	0.57	1.00	0.33	3.03	0.99
PVAD	*Omitted*				*Omitted*			
XVE	*Omitted*				*Omitted*			

Table 6: Logistic regression of pulmonary hypertension status at 3 and 6 months with pre-operative PVR as continuous variable.

We again applied logistic regression to the 3- and 6-months pulmonary hypertension status variable but used categorical PVR measurements instead of a continuous variable and the results are summarized in Table 7 below. As can be seen from the table, in this regression, all categories of pre-operative PVR (except >9 Wood Units which was omitted), implanting center, and HeartMate III LVAD were found to have a significant effect on pulmonary hypertension status at 3 months.

At 6 months, only the levels of pre-operative PVR were found to have a significant effect on PVR status, with the exception of those with pre-operative PVR > 9 Wood Units who had to be omitted from the regression. Similar to the 3-month regression, most LVAD types except for the HeartWare HVAD were excluded from the model as their inclusion predicted failure perfectly.

	3 Month Analysis				6 Month Analysis			
	Odds Ratio	**[95% Conf. Interval]**		**p-value**	**Odds Ratio**	**[95% Conf. Interval]**		**p-value**
Pre-Operative PVR								
<3	*Referent*				*Referent*			
3 to 5	28.01	5.98	131.24	**<0.01**	24.94	4.55	136.73	**<0.01**
5 to 7	68.99	11.00	432.57	**<0.01**	23.70	4.02	139.69	**<0.01**
7 to 9	48.67	4.34	545.61	**<0.01**	71.11	6.30	802.12	**<0.01**
>9	*Omitted*				*Omitted*			
Center								
Boston	*Referent*				*Referent*			
Halifax	13.36	3.00	59.43	**<0.01**	2.74	0.68	11.09	0.16
Sex								
Male	*Referent*				*Referent*			
Female	0.75	0.19	2.87	0.67	1.66	0.43	6.36	0.46
Age	1.03	0.99	1.08	0.14	1.03	0.98	1.07	0.25
Smoking	1.20	0.42	3.41	0.73	1.74	0.58	5.25	0.32
Hypertension	0.58	0.19	1.76	0.34	1.40	0.43	4.57	0.58
Diabetes	1.68	0.55	5.13	0.37	1.65	0.50	5.46	0.41
Dyslipidemia	0.80	0.20	3.26	0.76	0.53	0.12	2.46	0.42
Cardiomyopathy								
Ischemic	*Referent*				*Referent*			
Non-Ischemic	0.40	0.11	1.47	0.17	0.36	0.09	1.42	0.14
Ejection Fraction	1.01	0.93	1.10	0.81	0.93	0.84	1.02	0.11
Prior Cardiac Surgery	0.97	0.29	3.21	0.96	1.29	0.39	4.29	0.68
VAD Type								
HM2	*Referent*				*Referent*			
HM3	0.04	0.00	0.39	**0.01**	*Omitted*			
HVAD	0.51	0.14	1.88	0.31	0.79	0.22	2.90	0.72
PVAD	*Omitted*				*Omitted*			
XVE	*Omitted*				*Omitted*			

Table 7: Logistic regression of pulmonary hypertension status at 3 and 6 months with pre-operative PVR as categorical variable.

In order to assess our model, a receiver operating characteristics (ROC) curve was generated for the 3-month analysis logistic regression with PVR as a categorical variable.

The calculated area under the ROC curve was 0.89, suggesting relatively good discrimination of pulmonary hypertension status at 3 months with the variables included in our regression model.

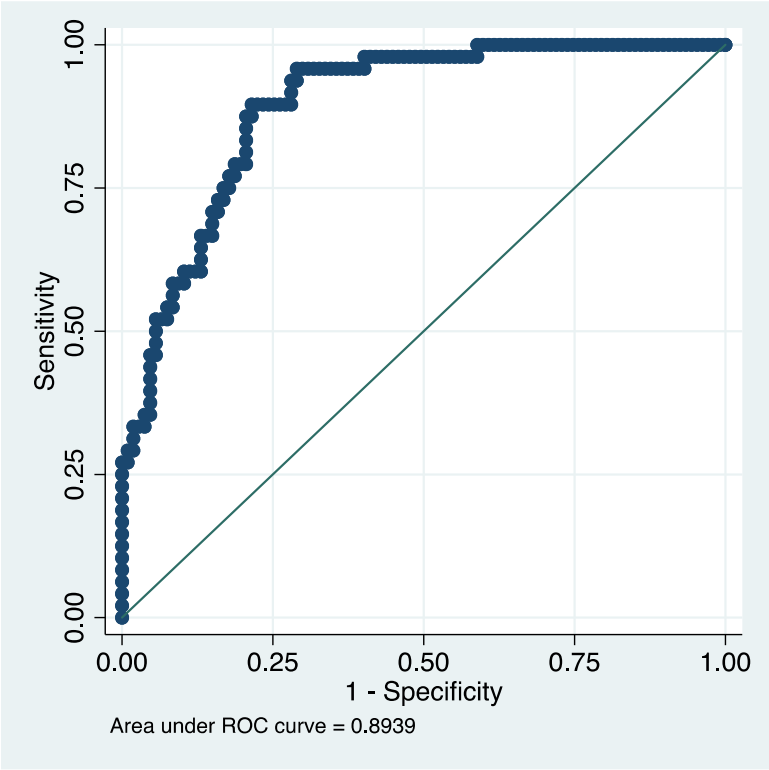

Figure 8: Receiver operating characteristic curve for logistic regression at 3 months post LVAD implant with PVR as categorical variable.

6 Discussion

6.1 Regional Practice Variability

One of the objectives of this study was to characterize the LVAD experience both in Halifax and at our partner institution in Boston. In addition to obtaining a snapshot of our LVAD patient population and implantation trends over the decade studied, our analysis also provided some insight into the differences between the two institutions. Despite having patient populations with similar mean age and gender composition, the Boston cohort appeared significantly more high-risk than their Halifax counterparts. Significantly more patients from Boston had pre-operative pulmonary hypertension in addition to more dyslipidemia and chronic obstructive pulmonary disease. These differences should not be surprising given the vastly different practice environments in Halifax and Boston.

Although we should not assume that our observations would be replicated on a national level, the single-payer Canadian healthcare system as opposed to the American multi-payer system means that patients may have had differing access to specialized services such as those required in advanced heart failure. Additionally, Halifax typically provides advanced heart failure surgery to most of the Atlantic provinces whereas the Brigham and Women's Hospital must compete with other institutions in the Boston area and so referral patterns will undoubtedly vary.

Interestingly, a far larger proportion of patients from Halifax were bridged to transplantation on device support compared to their counterparts from Boston (86% vs

54%, $p<0.01$). This may be a reflection of more deliberate patient selection in a Canadian system which has limited resources as opposed to a for-profit American healthcare system which generally accepted destination therapy with LVADs earlier than their Canadian counterparts[39].

Of note, the large number of HeartMate III devices implanted in the Boston cohort during the study period is likely secondary to special authorization for research purposes at this specific institution as the device was only approved for general use by the United States Food and Drug Administration in October of 2018[40]. Given that Health Canada also only approved the HeartMate III for general use in 2018[41] and that Halifax was not a participating institution for pre-market studies, none of these newer generation devices were implanted in Halifax patients during the study period.

6.2 Timeline of Pulmonary Hypertension Reversibility

Capturing longitudinal right heart catheterization measurements at various intervals allowed us to gain insight into the temporal trends observed in the reversibility of pulmonary hypertension while on LVAD support. As predicted, calculated PVR values decreased while on LVAD support and, for nearly half of patients with pre-operative pulmonary hypertension, normalization of their pulmonary pressures was attained within 3 months (See Table 3). This phenomenon continued over the period studied but the vast majority of patients who eventually had reversibility of their pulmonary hypertension experienced it by 6 months post LVAD implant.

Given that right heart catheterizations were only obtained as clinically indicated in our retrospective study, the actual proportion of patients who achieved normalization of their pulmonary pressures within the first three months of device support would likely be even higher if all patients had invasive hemodynamic measurements at regularly timed intervals.

Considering the above observation and the fact that LVADs are not without inherent risks or associated maintenance costs to our healthcare system, it would be reasonable to advocate for early assessment of pulmonary hemodynamics in order to determine transplant eligibility for selected patients in a timelier fashion.

6.3 Effect of Pulmonary Hypertension Magnitude on Reversibility

Despite the fact that reversal of elevated pulmonary vascular resistance while on LVAD support has been well established and reported in the literature, data on patients with very elevated pre-operative pulmonary vascular resistance remains scarce. In our observational study, we measured normalization of pulmonary hemodynamics in patients with very severe pre-operative pulmonary hypertension but there did appear to be a proportional effect size on PVR status based on the magnitude of pre-operative pulmonary hypertension as highlighted in Table 5. In other words, despite the fact that lower pre-operative pulmonary hypertension likely led to more rapid or lower post-operative pulmonary pressures, we did not identify a clear cut-off value for pre-operative PVR where one would not expect to see normalization of pulmonary hemodynamics following device implant and left ventricular offloading.

6.4 Maintenance of Reversibility Post Transplantation

In an exploratory analysis, patients who were successfully bridged to heart transplantation while on LVAD support were also followed for further changes to their pulmonary hemodynamics. While patients with pulmonary hypertension may have normalization of their pulmonary pressures and hence may be eligible for transplantation, some fear that their pulmonary vasculature remains pathological and hence they may experience recurrence of their pulmonary hypertension following transplantation. In our study population, with the exception of one patient, we did not observe an increase in calculated PVR following transplantation and outcomes appeared to be similar between those with and those without pre-LVAD pulmonary hypertension. This is in keeping with numerous recent studies that have found that long-term outcomes following transplantation appear to be the same whether patients have a history of pulmonary hypertension or not[42,43,44].

Of note, if a patient were to have experienced acute right ventricular failure and died as a consequence of elevated pulmonary arterial pressures following orthotopic heart transplantation, they would have been less likely to have undergone a right heart catheterization capturing rising pulmonary hemodynamics and so those measurements may not have been included in our analysis.

6.5 Disease Chronicity and Outcomes

We hypothesized that the etiology for the cardiomyopathy experienced by end-stage heart failure patients who go onto LVAD support would have an effect on the susceptibility of

their pulmonary vasculature for reversibility and normalization of pulmonary pressures but that did not appear to be the case. Our study patients were classified as either ischemic or non-ischemic etiology for their cardiomyopathy and this variable did not appear to have a significant effect on post-operative pulmonary hypertension in any of our regression models. Unfortunately, the retrospective nature of our data acquisition and the data captured in the institutional databases did not allow us to establish the length of time each patient was deemed to have advanced disease before being placed on device support, but it is possible that this would have yielded a correlation with post-operative pulmonary hemodynamic changes.

6.6 Impact of Device Selection on Pulmonary Hypertension

Interestingly, the choice of LVAD, specifically the implantation of the HeartMate III, appeared to be associated with a higher likelihood for normalization of PVR at 3 months in logistic regression (See Tables 6 and 7). Although this association was not present on every regression model, it is worth discussing as it could provide an opportunity for further research in this field. The HeartMate III LVAD is a newer-generation device which has numerous features that may portend hemodynamic benefits and hence could explain our observations. As opposed to some of the older axial-flow devices, the HeartMate III LVAD is a centrifugal pump that has a built-in pulsatility function which may have upstream effects on the pulmonary vasculature.

That being said, there are a few potential confounders which should be highlighted. Importantly, the HeartMate III device was only implanted in the Boston cohort during our

study period and hence the selection and management of these patients may have differed from those being treated in Halifax. Additionally, given that it is a newer pump which has only recently been available on the market, it is possible that a time confounder is present and perhaps implanting centers have simply become more discerning in patient selection and are choosing to implant devices in patients with a higher propensity for pulmonary hypertension reversibility or placing patients on mechanical circulatory support earlier in the natural history of the disease.

6.7 Limitations

Our study has a few limitations that should be reported. First and foremost, it is a retrospective observational study which has implied inherent biases. This treatment represents very advanced care which is only offered to highly selected individuals and so these results may not be applicable to the general heart failure population.

Given the multi-center analysis and regional referral patterns at both institutions, it was not practical to link our data to vital statistics from multiple provinces/states and as such mortality was not captured unless it occurred during the index hospitalization for LVAD implantation. As such, the best proxy for survival that was available given the nature of both databases and electronic records was the time of last right heart catheterization. However, this could have been misleading in survival analyses as patients who were doing well would be less likely to have invasive hemodynamic measurements and as such this was not included in our methods.

Additionally, given that our analysis relied on invasive hemodynamic measurements, patients had to have had clinical indications for such investigations in order to generate time points and hence a survival bias may have been present in that we only measured pulmonary pressures in patients who had survived to that point.

Finally, from a clinical perspective, our institutional databases did not provide information on pulmonary vascular reactivity (normalization of pulmonary vascular pressures with medical interventions) at time of right heart catheterization or on the prescribing and uptake of vasoactive medications which may also have affected pulmonary hemodynamics.

7 Conclusion

Given the increasing prevalence of advanced heart failure and limited organ availability for transplantation, rates of LVAD implantation have seen remarkable increases recently and this trend is expected to continue in the near future. Advanced heart failure can be associated with pulmonary hypertension which has traditionally been a contraindication to transplantation candidacy given the risk for early right ventricular failure and mortality following transplantation.

Multiple recent reports have suggested that LVAD support may reverse pulmonary hypertension and hence bridge patients to transplantation candidacy, but the timeline and factors associated with this physiological change have not been clearly defined.

Our study aimed to combine hemodynamic data on LVAD recipients at two heart transplantation institutions and examine longitudinal changes in pulmonary hemodynamics before and after LVAD insertion. Based on an analysis of 790 right heart catheterization in 177 patients treated with LVADs in Halifax and Boston over the study period, we have observed that the majority of patients with elevated pulmonary vascular resistance experience reversibility in the form of lowering pressures in the first 3 to 6 months of device support. Our analysis did not reveal a clear cutoff value of pre-operative PVR which would render reversibility impossible but rather a graduated and proportional effect modification was observed. Our various models did not identify any other clear pre-operative patient characteristic associated with subsequent changes in pulmonary hemodynamics but did suggest potential differences in device effect which would have to be further validated.

In summary, LVAD therapy for patients with end-stage heart failure and severe pulmonary hypertension appears to be effective in lowering pulmonary vascular resistance and provides a therapeutic pathway to transplant candidacy. Furthermore, a significant amount of reversibility appears to be evident in the first 3-6 months of device support and so early reassessment with right heart catheterization when clinically appropriate may allow patients on device therapy to be listed for transplantation early and may spare them from unnecessary risks with prolonged mechanical circulatory support.

Finally, based on our limited observations, the pulmonary hypertension reversibility experienced while on LVAD support appears to persist following transplantation which suggests that patients with pre-operative pulmonary hypertension may have similar post-transplant prognosis compared to their normotensive peers.

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