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Elderly Patients Bridged from Left Ventricular Assist Devices to Heart Transplant are not at Increased Risk

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Abstract

Introduction: Outcomes in patients undergoing Ventricular Assist Device (VAD) implant continue to improve with excellent long-term survival and improving adverse event profiles. However, skepticism remains in transplanting elderly patients from VADs implanted as bridge to transplant, given concern over the complexity of the operation and post-operative recovery. We hypothesized that elderly (65 years of age and older) patients on VAD support could successfully be transplanted with minimal morbidity and mortality.

Methods: We retrospectively analyzed the UNOS adult heart transplant donor and recipient data from June 2004 to December 2013, during which 6,793 Orthotopic Heart Transplants (OHT) were performed in patients older than 65 years of age. The recipients were divided into two cohorts: BTT with continuous flow LVAD (n=329) or non-VAD (n=6,265). Patients with an RVAD, total heart, biventricular assist device, or multi-organ transplant were excluded (n=199). Statistical analyses included descriptive statistics and Kaplan-Meier survival analyses.

Results: No differences existed with regard to recipient gender (p=0.14), total waitlist time (p=0.14), history of chronic obstructive pulmonary disease (p=0.07), or prior transfusions (p=0.36). Donors did not differ with regards to age (p=0.09), gender (p=0.11) or left ventricular ejection fraction (p=0.59). The BTT recipients' allografts had a significantly longer ischemic time (p=0.02). Post-operatively, there was a significantly higher incidence of dialysis within the non-VAD cohort (9.7%) compared to BTT cohort (6.3%, p=0.04). The incidence of cardiac re-operation (p=0.32), stroke (p=0.34), infection (p=0.11) and heart block (p=0.31) were similar. The rate of rejection was low without significant differences amongst the cohorts (8.7% *vs.* 6.1%, p=0.07). There was no difference in length of hospital stay (p=0.11). One (90% *vs.* 85%) and five-year (69% *vs.* 71%) survival was similar in the BTT and non-VAD cohorts, using Kaplan-Meier Survival Analysis (log rank p=0.1090).

Conclusion: Appropriately selected patients ≥ 65 years of age, bridged with an LVAD have a survival comparable to those patients without an LVAD, post-orthotopic heart transplant. The benefits of VAD as BTT should be considered in patients 65 and older to allow stabilization for subsequent OHT.

Keywords: Heart transplant; Left ventricular assist device; Bridge to transplantation

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Abbreviations

BTT: Bridge to Transplantation; LVAD: Left Ventricular Assist Device; UNOS: United Network for Organ Sharing; OHT: Orthotopic Heart Transplant; BMI: Body Mass Index; PRA: Panel Reactive Antibody

Introduction

Heart failure remains a major health concern with approximately 5.7 million individuals suffering in the United States alone [1]. Orthotopic Heart Transplantation (OHT) is currently the gold standard treatment for heart failure. However, given the discordant number of patients on the wait list compared to the availability of donor hearts, an increasing number of patients are being Bridged to Transplant (BTT) using Left Ventricular Assist Devices (LVAD) [2-4]. Numerous studies have demonstrated excellent post-transplant outcomes, without concern for reduced mortality or morbidity in younger patients bridged to transplant [5-8]. For older patients, however, there is a greater concern with respect to post-transplant outcomes following VAD implant given the higher incidence of co-morbidities. Consequently, age is often a relative or absolute contraindication for

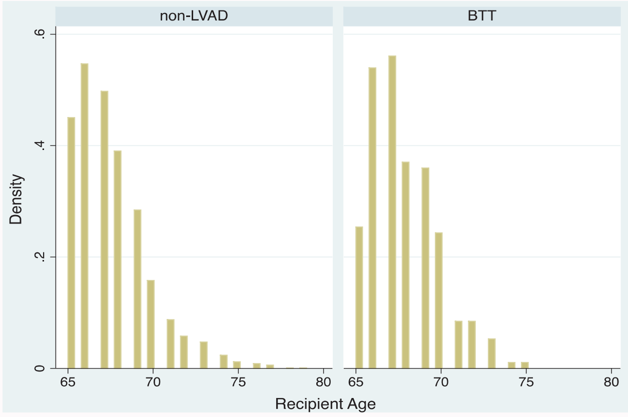

Figure 1: Age distribution density for recipients 65 years of age and older stratified by Bridging to Transplantation with a LVAD (BTT) or direct transplantation without VAD (non transplantation with an LVAD (BTT) or direct transplantation without VAD (non-VAD).

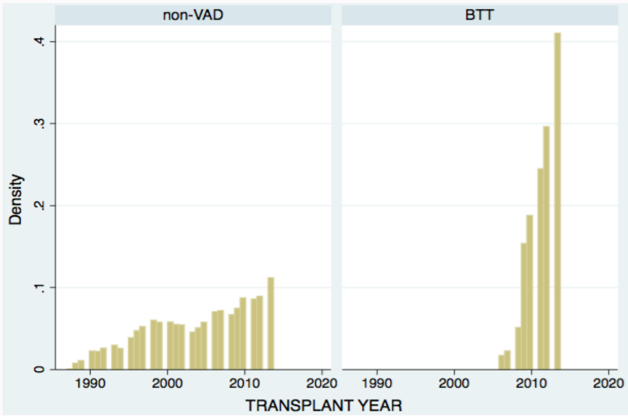

Figure 2: Year of transplantation distribution density of recipients 65 years of age and older stratified by Bridging to Transplantation with an LVAD (BTT) or direct transplantation without VAD (non-VAD).

transplant listing in the presence of an LVAD. Studies focusing on the use of LVAD as BTT in patients 65 years of age or older have been limited. The studies have generally included both early pulsatile-flow and continuous-flow LVADs [9-11]; as a result, the conclusions have been confounded and difficult to interpret. They have often concluded that elderly patients should not undergo transplantation from a VAD platform. The largest study to date by Allen et al. [12] noted that patients older than 60 years of age with a VAD had decreased short term survival compared to those patients directly transplanted, supporting VAD as a contraindication to transplant in the elderly. However, with improvements in device technology and increasing experience with patient selection, intra operative management, operative technique and postoperative care, this conclusion to not transplant elderly patients from a VAD platform is brought into question. This is further supported by a recent small cohort study that demonstrated excellent survival after heart transplantation in elderly patients with continuous-flow LVAD [13,14].

Given the growing elderly population, an increasing burden of ischemic heart disease and improving medical therapy, the prevalence of end-stage heart failure in older patients will continue to rise. If we are to continue to offer heart transplantation to a wide range and age of patients, it is vital to elucidate the risk profile associated with transplant post-VAD. Thus, it is essential to examine the outcomes for older patients with LVADs whom are bridged to transplantation. The objective of this study is to directly compare both short- and long-term post-transplant all-cause mortality in a large cohort of patients using the United Network for Organ Sharing (UNOS) database inpatients 65 years of age or older who received a continuous flow LVAD as BTT to those patients directly transplanted without a VAD. We hypothesized that patients ≥ 65 bridged to transplant would have equivalent outcomes to patients who were directly transplanted.

Methods

Data source

Data from the UNOS registry of heart transplant recipients between June 2004 and December 2013 were utilized for analysis. De-identified data from the Standard Transplant Analysis and Registry and the follow-up files were merged to create a cohort of patients with heart failure who received heart transplantation. A retrospective cohort analysis was conducted to determine the post-transplant survival in patients 65 years of age and older that were either BTT or directly transplanted without a VAD.

Sample

The study sample was limited to adult patients (65 years of age and older) with heart failure listed for heart transplantation after June 2004. Only patients with FDA approved continuous flow LVADs in the UNOS dataset were analyzed (HeartMate II LVAD Thoratec Corp, Pleasanton, CA and HeartWare, Framingham, MA). Patients were excluded if they were undergoing multi-organ transplantation. The primary outcome was all cause mortality after OHT. Rejection

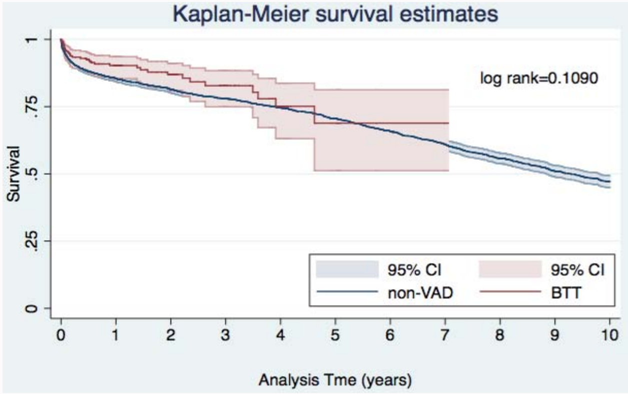

Figure 3: Kaplan-Meier analysis demonstrating cumulative survival for recipients 65 years of age and older stratified by Bridging to Transplantation with a LVAD (BTT) or direct transplantation without VAD (non-VAD) (log rank p=0.1090).

Patients at risk per respective time point

	Implant	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
BTT	239	138	90	48	24	10	3	…	…	…	…
Non-VAD	3,859	2,923	2,554	2,231	1,921	1,644	1,377	1,125	920	746	618

episodes in the first post-operative year and short-term mortality were also examined.

The timing of data collection for the BTT cohort occurred once the patient was listed for transplantation. Data collection from LVAD implantation, immediate post-operative LVAD implant and bridge to determination is not included in the UNOS database.

Outcome and covariates

The primary outcome of this study is post heart transplant mortality from any cause. All-cause mortality was based on the last follow-up status of a recipient after heart transplantation. Recipient and donor variables, including age, sex, BMI, renal function, allograft ischemic time, and infectious serologies were additionally analyzed.

Statistical analysis

Baseline characteristics were compared between BTT and non-VAD by one-way analysis of variance (continuous variables) and X^2 tests (categorical variables). Multivariate analyses were performed using Cox proportional hazard models to assess the independent effect of the BTT modality on mortality. Patients were censored if they were lost to follow-up. Logistic regression assessed the odds of a rejection episode in the years after heart transplantation. Variables associated with morality on exploratory analyses ($p<0.1$) were incorporated into the final model. The final model included BTT, sex, age, BMI, creatinine level, bilirubin level, wait list status, history of diabetes, use of ventilator and IABP prior to transplant, recipient functional status, donor age, donor gender, donor BMI, donor left ventricular function, and ischemic time. For all analyses, $p \leq 0.05$ (2-tailed) was significant. Means are presented with standard deviations and medians with interquartile ranges and hazard ratios and Odds Ratios (ORs) with 95% Confidence Intervals (CI). No assumptions were used for the missing data. Data was missing completely at random and hence list-wise deletion was implemented as the preferred method of handling this data. When data were missing, the presented percentages and mean were those of available data. All statistical analyses were completed with STAT 14.1 (College Station, Texas).

Results

Study population and demographics

A total of 37,408 adult heart transplants were performed in the United States between June 30, 2004 and December 31, 2013. A subgroup analysis of patients 65 years of age and older, revealed 6,793 OHTs were performed during this time frame. Patients who had a right ventricular assist device, total artificial heart, biventricular device, or received a multi-organ transplant were excluded from the analysis (n=199). The remaining patients were then stratified into 2 groups: 1) those bridged to transplant with a continuous flow LVAD (BTT, n=329) and 2) patients transplanted without a VAD (non-VAD, n=6,265).

Recipient pre-operative characteristics

Analysis of pre-operative recipient variables revealed a statistically significant but clinically unappreciable difference in age between BTT and non-VAD cohorts (67.8 ± 2.0 *vs.* 67.5 ± 2.2 years, p=0.03) (Table 1, Figure 1). The BTT cohort had a significantly higher BMI (27.2 kg/m^2 ± 4.4 kg/m^2 *vs.* 25.4 kg/m^2 ± 3.9 kg/m^2, p=0.0001). The median waitlist time between the groups was equivalent (p=0.14). The BTT cohort had a significantly higher incidence of diabetes when compared to the non-VAD group (36.9% *vs.* 19.0%, p=0.01). Only 25.9% of the non-VAD transplant patients underwent prior cardiac surgery, while the entire BTT cohort had at least 1 prior operation (p=0.001). As shown in (Figure 2), the transplantations of the BTT cohort were performed at a significantly later time period than the non-VAD cohort (p=0.0001).

The incidence of prior transfusions was not significantly different between the cohorts (p=0.36). No difference was observed in the Panel Reactive Antibody (PRA) sensitization between the cohorts. The median value of the peak class I PRA value was 15% (interquartile range: 6, 47) in the BTT group compared to 15% (6, 38) in the non-VAD group (p=0.89). Similarly, no difference in the peak class II PRA values was observed between the groups (p=0.35).

As expected, the BTT patients had a significantly higher cardiac output than the non-VAD (4.6 L/min ± 1.3 L/min *vs.* 4.2 L/min ± 1.3 L/min, p=0.0001), though given a lower BMI in the non-VAD cohort, this difference is likely of marginal significance. A lower mean pulmonary artery pressure (27.3 mmHg ± 9.8 mmHg *vs.* 30.0 mmHg ± 9.6 mmHg, p=0.0001) and pulmonary capillary wedge pressure (17.2 ± 9.1 *vs.* 20.2 ± 8.5, p=0.0001) was observed in the BTT cohort.

Table 1: Baseline characteristics of patients older than 65 years of age stratified by the presence of a continuous flow left ventricular assist device as Bridge to Transplant (BTT) or transplant without ventricular assist device support (non-VAD).

	BTT	Non-VAD	p
Recipient			
Age, year	67.8 ± 2.0	67.5 ± 2.2	0.03
Gender (male), n (%)	290 (88.2)	5,339 (85.2)	0.14
BMI, (kg/m^2)	27.2 ± 4.4	25.4 ± 3.9	0.0001
Total waitlist time, (days)[a]	122, (37, 257)	93 (28, 275)	0.14
Waitlist Status, n (%)			0.0001
1	315(100)	2,167 (35.7)	
2	0 (0.0)	3,272 (53.9)	
PRA %, peak Class I	15 (6,47)	15 (6, 38)	0.89
PRA %, peak Class II	17 (3 ,27)	11 (3, 40)	0.35
Preoperative Lab Values			
Total bilirubin (mg/dL)	1.1 ± 2.0	1.2 ± 2.5	0.01
Creatinine (mg/dL)	1.3 ± 0.5	1.5 ± 1.0	0.002
Albumin (g/dL)	3.63 ± 0.60	3.68 ± 0.71	0.21
Hemodynamics			
Cardiac output (L/min)	4.6 ± 1.3	4.2 ± 1.3	0.0001
Mean pulmonary pressure (mmHg)	27.3 ± 9.8	30.0 ± 9.6	0.0001
Pulmonary wedge pressure (mmHg)	17.2 ± 9.1	20.2 ± 8.5	0.0001
Past Medical History, n (%)			
Diabetes	121 (36.9)	1,041 (19.0)	0.01
Chronic obstructive pulmonary disease	1 (0.3)	122 (4.4)	0.07
Peripheral vascular disease	0 (0.0)	112 (4.1)	0.06
Previous transfusions	2 (0.7)	864 (30.7)	0.36
Prior cardiac surgery	329 (100)	1,580 (25.9)	0.001
Blood Type, n (%)			0.02
A	118 (35.9)	2,600 (41.5)	
AB	11 (3.3)	290 (4.6)	
B	39 (11.9)	766 (12.2)	
O	158 (48.0)	2,582 (41.2)	
Support Immediately Prior to Transplant, n (%)			
Extracorporeal membrane oxygenation	0 (0.0)	26 (0.6)	0.71
Intra-aortic balloon pump	5 (1.5)	289 (4.6)	0.01
Inotropic support	27 (8.2)	2,059 (32.9)	0.0001
Ventilator	0 (0.0)	51 (3.1)	0.04
Intensive care unit	0 (0.0)	508 (51.7)	0.001

[a]Median (interquartile range)

Immediately prior to transplant, the non-VAD group required advanced support for hemodynamic stabilization, with increased use of an intra-aortic balloon pump (p=0.01), inotrope infusion (p=0.0001) and ventilator support (p=0.04).

Using the Karnofsky performance status scale, patients are able to be classified as to their functional impairment [15]. A lower Karnofsky score correlates with a reduced prognosis. When examining the functional status between the two cohorts, a statistical difference was noted (Table 2). The two largest functional statuses in the BTT cohort were 17.7% at 70% activity-Cares for self unable to carry on normal activity or active work and 15.2% at 80% activity-normal activity with effort: some symptoms of disease. However, in the non-VAD cohort, the two greatest functional statuses were 10.3% at 70% activity and 9.2% at 20% activity-Very sick, hospitalization necessary: active treatment necessary (p=0.0001).The difference between the groups suggest that patients in the non-VAD cohort had greater functional impairment when compared to the BTT cohort.

Donor allograft criteria

Donor allograft variables were largely similar between cohorts, though certain key difference existed, (Table 3). A higher Body Mass Index (BMI) was present in the allograft donors to the BTT cohort (27.6 km/m^2 ± 5.3 km/m^2 *vs.* 26.3 km/m^2 ± 5.6 km/m^2, p=0.0001). The median allograft ischemic time was longer in the BTT cohort at 3.3 hours (2.4, 4.0) compared to 3.1 hours (2.4, 3.8, p=0.02). Both

Table 2: Pre-transplantation functional status of patients older than 65 years of age stratified by the presence of a continuous flow left ventricular assist device as Bridge to Transplant (BTT) or transplant without ventricular assist device support (non-VAD).

	BTT	Non-VAD	p
Functional Status, n (%)			0.0001
10% - Moribund, fatal processes progressing rapidly	1 (0.3)	40 (0.7)	
20% - Very sick, hospitalization necessary: active treatment necessary	27 (11.3)	557 (9.2)	
30% - Severely disabled: hospitalization is indicated, death not imminent	23 (7.0)	249 (4.1)	
40% - Disabled: requires special care and assistance	36 (11.0)	236 (3.9)	
50% - Requires considerable assistance and frequent medical care	40 (12.2)	400 (6.6)	
60% - Requires occasional assistance but is able to care for needs	49 (14.9)	507 (8.4)	
70% - Cares for self: unable to carry on normal activity or active work	58 (17.7)	626 (10.3)	
80% - Normal activity with effort: some symptoms of disease	50 (15.2)	365 (6.0)	
90% - Able to carry on normal activity: minor symptoms of disease	30 (9.2)	71 (1.2)	
100% - Normal, no complaints, no evidence of disease	3 (0.9)	17 (0.3)	

Table 3: Donor demographics for allografts to patients older than 65 years of age stratified by the presence of continuous flow left ventricular assist device (BTT) or direct transplantation without a VAD (non-VAD).

	BTT	Non-VAD	p
Age, years	32.2 ± 11.7	33.9 ± 13.3	0.09
Gender (male), n (%)	178 (73.3)	2,672 (68.4)	0.11
BMI, (kg/m^2)	27.6 ± 5.3	26.3 ± 5.6	1.00E-04
Graft ischemic time, (hours)[a]	3.3 (2.4, 4.0)	3.1 (2.4, 3.8)	0.02
Distance, (miles)[a]	93.8 (9.1, 302.6)	83.7 (12.6, 251.5)	0.42
Past Medical History, n (%)			
Hypertension	40 (16.5)	548 (15.8)	0.81
Diabetes-insulin dependent	4 (50.0)	51 (42.9)	0.69
CDC high-risk donor	28 (11.5)	219 (10.4)	0.75
Cause of Death, n (%)			0.001
Anoxia	64 (26,4)	484 (12.4)	
Cerebrovascular/stroke	53 (21.8)	1,157 (29.7)	
Head trauma	115 (47.3)	2,025 (52.0)	
CNS tumor	2 (0.8)	42 (1.2)	
Other	9 (3.7)	190 (4.9)	
Laboratory Value			
pH[a]	7.41 ± 0.06	7.41 ± 0.14	0.59
Blood urea nitrogen, (mg/dL)[a]	18.3 ± 12.3	16.5 ± 14.5	0.001
Creatinine, (mg/dL)[a]	1.5 ± 1.5	1.3 ± 1.3	0.01
Aspartate aminotransferase, (u/L)[a]	111.9 ± 310.4	91.5 ± 331.4	0.63
Alanine aminotransferase, (u/L)[a]	99.9 ± 218.1	98.3 ± 301.3	0.4
Total bilirubin, (mg/dL)[a]	1.1 ± 1.5	1.2 ± 1.6	0.11
Hemodynamics			
LV ejection fraction, (%)[a]	60 (55, 65)	60 (55, 65)	0.6
Mean arterial pressure, (mmHg)[a]	83.6 ± 20.8	83.7 ± 21.4	0.9
Central venous pressure, (cmH_2O)[a]	9.3 ± 3.1	9.1 ± 3.6	0.52
Pulmonary capillary wedge pressure, (mmHg)[a]	14.2 ± 6.4	12.5 ± 5.0	0.19
Cardiac index, ($L/min/m^2$)[a]	4.7 ± 0.9	4.3 ± 1.5	0.08
Cardiac output, (L/min)[a]	8.9 ± 2.2	8.1 ± 2.4	0.06

[a]Median (interquartile range)
BMI: Body Mass Index; PRA: Panel Reactive Antibody.

Table 4: Post-OHT outcomes in recipients older than 65 years of age, stratified by BTT or direct transplantation (non-VAD).

Complications	BIT	Non-BIT	p
Stroke	10 (4.2)	80 (2.3)	0.3
Dialysis	15 (6.3)	342 (9.7)	0
Surgical operation-any	1 (0.3)	251 (13.4)	0.4
Permanent pacemaker	6 (2.5)	136 (3.9)	0.3
Drug treated infection	2 (0.6)	445 (23.8)	0.1
Cardiac Re-Operation	1 (0.3)	201 (10.7)	0.3
Length of Stay(OHT to discharge, days)	15 (11, 23)	14 (10, 23)	0.1
Acute Rejection Episode, n (%)	18 (7.5)	130 (6.1)	0.1
Cause of Death, n (%)			0.3
Infection: bacterial septicemia	4 (12.1)	121 (7.1)	
Multiple organ failure	5 (15.2)	147 (8.6)	
Cardiovascular: cardiac arrest	1 (3.0)	98 (5.7)	
Renal failure	0 (0.)	81 (4.8)	
Other	2 (6.1)	116 (6.8)	
Unknown	1 (3.0)	213 (12.5)	

[a]Median (interquartile range)

Table 5: Univariate and multivariate predictors of 1-Year mortality in patients 65 years of age and older.

	Univariate Analysis		Multivariate Analysis	
Variables of Interest	HR (95% CI)	p Value[a]	HR (95% CI)	p Value[b]
BTT	0.90 (0.21-3.77)	0.88	0.74 (0.16-3.33)	0.7
non-VAD	Reference		Reference	
Additional variables				
Male sex	2.24 (1.03-4.90)	0.04	1.36 (0.42-4.38)	0.61
Age	1.12 (0.94-1.36)	0.21	1.03 (0.82-1.31)	0.75
Recipient BMI	0.99 (0.91-1.08)	0.95	–	
Recipient creatinine level	1.31 (0.59-2.94)	0.51	1.48 (0.49-4.51)	0.49
Recipient total bilirubin level	1.29 (0.71-2.36)	0.4	1.18 (0.68-2.10)	0.56
Wait list status	0.99 (0.99-100)	0.67	–	
Recipient history of diabetes	0.99 (0.99-100)	0.25	1.01 (0.69-1.48)	0.96
Pre-OHT ventilatory support	0.18 (0.02-1.48)	0.11	–	
Pre-OHT IABP	0.89 (0.21-3.79)	0.89	–	
Recipient functional status	1.00 (0.99-1.00)	0.2	–	
Donor age	1.01 (0.98-1.03)	0.61	–	
Donor gender	0.90 (0.41-1.95)	0.78	–	
Donor BMI	1.06 (0.98-1.16)	0.15	1.02 (0.93-1.11)	0.66
Donor left ventricular ejection				
fraction	0.97 (0.91-1.02)	0.28	0.97 (0.91-1.03)	0.36
Ischemic time	0.91 (0.65-1.29)	0.6	0.59 (0.40-0.87)	0.01

[a]p value based on univariate Cox proportional hazard analysis. [b]p value based on multivariate Cox proportional hazard regression. The final model incorporated the following covariates: recipient sex, recipient age, recipient creatinine level, recipient total bilirubin level, recipient ventilatory support, donor BMI, and allograft ischemic time. Final model performed with 3,429 observations.

allograft cohorts demonstrated excellent and similar left ventricular function (60% *vs.* 60%, p=0.59). No significant difference was observed between the central venous pressure (p=0.52) and the median pulmonary capillary wedge pressure (p=0.19). The cardiac index of the BTT donors was noted to be higher, although not significantly different than non-VAD donors (4.7 L/min/m^2 ± 0.9 L/min/m^2 *vs.* 4.3 L/min/m^2 ± 1.5 L/min/m^2, p=0.08).

Post-operative outcome measurements

For the majority of post-operative measures of morbidity, the outcomes were similar between the groups (Table 4). There was a higher incidence of acute kidney injury requiring dialysis within the non-VAD group (9.7%) compared to the BTT group (6.3%, p=0.04). There was no significant difference in the incidence of stroke (p=0.34), permanent pacemaker requirement (p=0.31), infection (p=0.11), and cardiac re-operation (p=0.32). Furthermore, there was no difference in the frequency of allograft rejection within the index hospital stay (p=0.07). Examining the cause of death, there was no significant difference between the two groups (p=0.28). The three most common listed causes of death were multiple organ failure (15.2%), infection septicemia (12.1%) and cardiovascular arrest (3.0%) within the BTT cohort. For the non-VAD cohort, the three most common causes of death were multiple organ failure (8.6%), infection bacterial septicemia (7.1%) m and cardiovascular arrest (5.7%).

Survival

One-year survival (90% *vs.* 85%), three-year survival (83% *vs.* 78%) and five-year survival (69% *vs.* 71%) was similar in the BTT and non-VAD cohorts. Kaplan-Meier survival curves with corresponding log-rank analyses demonstrated no significant difference in patient survival between the groups (log rank p = 0.1090) (Figure 3).

Multivariable analysis

After risk adjustment using multivariate Cox proportional hazard regression (n=184), in BTT patients older than 65 years of age, there was a trend toward decreasing the hazard 1 year-mortality, but this did not reach statistical significance (HR 0.90; 95% CI, 0.21-3.77, p=0.88) as shown in Table 5. Additional covariates impacting the risk of first year death in patients older than 65 years of age were recipient sex, recipient BMI, recipient creatinine level, and recipient total bilirubin level, intra-aortic balloon pump prior to transplantation, recipient functional status and donor age. On multivariate analysis, there was a significant impact of ischemic time observed (p=0.01).

Discussion

End-stage heart failure in patients older than 65 years of age remains a difficult entity to treat given high rates of patient co-morbidities and the absence of well-defined therapeutic guidelines for this population. Despite equivocal post-transplant outcomes in patients older than 65 years of age [9,16-21] and increasing experience of bridge to transplantation LVAD therapy [22], the practice of transplanting BTT patients older than 65 years of age remains uncommon. Prior evidence has demonstrated that age is a significant risk factor for mortality and poor survival post transplantation [23]. Other studies, however, have not supported the effect of age on survival [9,24,25]. The current study determined that age is not predictive of post-transplantation survival in the BTT population of patients; therefore, age itself should not be considered an absolute risk for transplantation.

This study examined outcomes after OHT in patients 65 years of age or older by BTT modality using the UNOS database. The patients examined were limited to the two most commonly implanted continuous flow LVADs: St. Jude HeartMate II and HeartWare HVAD. In this study, older patients who received a continuous flow LVAD had equivalent one and five year survival compared to those who underwent direct transplantation without a VAD. Albeit, there was a clear selection bias that is inherent in this study in that only those patients who are hemodynamically stable and with minimal post-VAD morbidities, were ultimately selected for transplantation. Nonetheless, the results appear to clearly support heart transplant as a viable therapeutic option to improve quality of life and long-term survival in patients 65 years of age and older. With regards to an upper limit of transplantation, as shown in (Figure 1), the majority of transplantation is performed in those patients ages 65-70 with a precipitous drop off after the age of 70. As a result, the conclusions of this study are readily applied to those patients 65-70. The results of this study are in contrast to those by Allen et al. [12], who in their multi-institutional study from 2005 to 2010, found a reduced 30-day and 1-year survival within the BTT population older than 60 years of age compared to the direct transplantation either with or without inotropic support. However, when Allen et al. [12] results were conditioned on surviving 30-days after OHT, the 1-year survival differences by BTT modality were no longer significant. The differences between the current study and this earlier study may be related to the later time period of examination using improved VAD technology with smaller pumps as well as enhanced surgical techniques in regards to VAD explant. Moreover, the BTT modality in this study was not associated with increased rejection within the first year. This result suggests that VADs are not associated prohibitive sensitization, as has been implied in numerous reports [12,26,27].

In addition to an assessment on patient outcomes, the current study also highlights the inherent difference between patients who are bridged to transplant with an LVAD and those who receive a heart transplant without VAD. The BTT cohort had a higher BMI than the non-VAD heart transplant patient population and was more commonly blood type O. Both of these factors contribute to the increased difficulty and perhaps longer waitlist time to find a suitable donor for large blood type O patients. Interestingly, while VAD patients pose increased operative risk given the sternal reentry and VAD explant, this was counterbalanced by enhanced physiologic support for the non-VAD cohort as related to the reduced need for ICU care, intubation, intravenous inotropic support, and reduced functional status that may similarly increase risk.

Based upon the findings of this study, it appears that given the choice of either advanced medical support (i.e. IABP, inotropes, ICU, etc.) or VAD as BTT, strong consideration should be given for early VAD implant. This is especially true in the traditionally difficult to transplant subgroup of large patients with blood type O or those who are highly sensitized. Furthermore, it must be recognized that VAD as BTT is likely increasingly important in those regions where allografts availability is in extreme shortage. While these principles are clearly pursued in young patients, it appears to be somewhat controversial in older patients. Based upon the findings presented here in, we strongly advocate for following similar VAD implant principles in older transplant candidates, given excellent post-transplant outcomes in appropriately selected patients. This finding and thought is in contrast to that of those who suggest that subjecting an elderly patient to two major cardiac operations would expose those patients to an increased risk and therefore advocate for advanced medical therapy while on the wait list [28].

Interestingly, the incidence of post-operative complications within both cohorts was low. The only significant difference between the two groups was a 3.4% higher incidence of acute renal failure immediately post-operatively requiring dialysis in the non-VAD cohort. Prior work has supported a higher rate of dialysis within BTT cohorts [9]; however, between these two cohorts, a higher incidence was observed within the non-VAD group. This difference is likely reflected by the improved hemodynamic stabilization with higher cardiac outputs and reduced pulmonary artery pressures within the BTT cohort translating into improved end organ function within this study population. Additionally there was no significant difference in the cause of death observed amongst the cohorts. There was a trend towards a higher rate of infection-bacterial septicemia within the

LVAD group compared to the non-VAD group. Given the small sample size, it is difficult to assess whether the higher incidence of septicemia is related to prior LVAD driveline infections or possible central line catheters. Furthermore, the use LVADs is known to vary greatly within the United States [29]; however, when examining the UNOS database for the study population there is no difference in those patients 65 years of age or older who were BTT *vs.* directly transplanted. As the use of LVADs continue to expand within all patients, it is essential that increased use occurs broadly and not regionally.

In conclusion, it is essential to note that the patients who are chosen for heart transplantation following LVAD have undergone a rigorous evaluation process. The patients are first screened for the criteria to meet LVAD implantation. They then must have improvement in their hemodynamics with limited complications in order to be selected for heart transplantation. This study did not aim to exam which patients 65 years of age would be ideally selected for BTT but rather if it was safe. Future studies should aim to exam what factors in particular those following LVAD implantation but prior to heart transplantation make a patient an ideal candidate with excellent survival post transplantation.

Our study has built upon the prior work for the investigators using a multi-institutional cohort. This series provides a snapshot of the current practices in the United States and demonstrates that patients 65 years of age and older who are bridged to transplant with an LVAD have an equivalent survival to those are directly transplanted without a VAD. The current study presents data to support the notion that age is not an independent risk factor and thus patients who may have a prolonged waitlist time should be considered for possible bridge with an LVAD.

Conclusions

Patients greater than 65 years of age can be safely bridged to transplantation with a continuous flow left ventricular assist device without significant increases in morbidity and mortality. The outcomes are associated with comparable long-term survival post-transplantation compared to primarily transplanted patients.

Limitations

Of the total heart transplants performed during the study period, the number of isolated heart transplant in patients older than 65 year of age is 22.2%. When divided into the two study cohort, only 5.2% of the patients 65 years of age or older are bridge to transplantation and 17% of the patients 65 years of age and older are directly transplanted. Although this is a small percentage of the population, it is a largest to date with our aim of this study showing that this patient population can safely undergo a BTT to heart transplantation strategy. Furthermore, Given that distribution of the transplantation patients is largely focused on patients between the ages of 65 and 70, care should be used in inferring that transplantation can safely be performed for BTT patients as well as non-VAD patients for those older than 70 years of age.

The timing of data collection within the UNOS database occurs once the patients are listed for transplantation. In particular, the BTT cohort, the time period around LVAD implantation and listing as bridge to destination is not included in the database. In particular, for the blood transfusions, there is likely a low reporting within the LVAD cohort. Despite this low incidence of reporting, there was no observed increase in the PRA level within the BTT or with acute episodes of rejection within the BTT cohort compared to the non-VAD cohort.

Additionally, although all data in the UNOS database is entered by trained personnel using standardized data collection forms, there is a potential for data entry errors, which could introduce inaccuracy to our findings. In addition, large administrative databases such as UNOS, often suffer from some amount of missing data. Given the missing data was not constant across variables, imputation of data was not used in order not discard data. Second, although multivariate Cox proportional hazard modeling was used to adjust for confounding, it is understood that residual confounding may remain even after accounting for those factors in our model. Our analysis includes only the most commonly implanted continuous-flow LVADs. Although this was intentional to increase the homogeneity of the study cohort, this could limit the generalizability. And finally, future studies should be performed to examine the outcomes of those patients initially older than 65 years of age whom were initially selected as BTT but then did not have a transplant.

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