**Impact of wait times for cardiac transplantation on outcomes after implantation of left ventricular assist devices (LVAD)**

**Running Title: OHT timing and characteristics after LVAD placement**

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**Abstract**

**Background -** The optimal timing for orthotopic heart transplantation (OHT) after the implantation of left ventricular assist devices (LVAD) is unknown. In determining the optimal time for OHT after LVAD, the need for clinical stability and time to recover from major surgery is balanced by the risk of LVAD complications and the formation of adhesions and scarring. Some have argued that performing OHT early after LVAD placement poses an increased risk of morbidity and mortality to patients. In this study, we describe the timing and outcomes of LVAD implantation and the impact of invasive hemodynamic monitoring and timing of post-LVAD OHT on in-hospital survival in the United States.

**Methods -** Using data from the Nationwide Inpatient Sample (NIS) from 1998 to 2011, we identified patients 18 years of age or greater who underwent implantation of a LVAD and for which the date of procedure was available. We calculated in hospital mortality for those patients who underwent OHT during the same hospitalization as a function of time from LVAD to OHT, adjusting for age, sex, race, household income, and number of comorbid diagnoses. We also compared in hospital mortality for those patients who underwent LVAD placement without OHT to mortality for patients who underwent OHT after LVAD placement. Finally, we analyzed the effect of time to OHT after LVAD placement on the length of hospital stay post-transplant.

**Results** - 2200 patients underwent implantation of a LVAD in this cohort. 164 (7.5%) patients also underwent OHT during the same hospitalization, which occurred on average 32 days (IQR 7.75 - 66 days) after LVAD implantation. Of patients who underwent OHT, patients who underwent transplantation within 7 days of LVAD implantation (‘early’) experienced increased in-hospital mortality (26.8% vs. 12.2%, p = 0.0483) compared to patients who underwent transplant after 8 days (‘late’).There was no statistically significant difference in patient demographics between the early and late groups with regards to age, sex, race, household income, or number of comorbid diagnoses. Compared to patients who underwent LVAD implantation but did not undergo OHT, patients who underwent late OHT after LVAD had decreased mortality (12.2% vs. 27.0% p < 0.001). Patients who underwent early OHT after LVAD did not show a similar mortality benefit (26.8% vs. 27.0%, p = 0.946). Patients who underwent OHT were younger than patients who did not undergo OHT (48.2 vs. 55.3 years, p < 0.001), but were not statistically significantly different with regard to sex, race, household income, or the number of comorbid diagnoses. Post-transplant LOS after LVAD placement was not significantly different between patients who underwent early OHT and patients who underwent late OHT.

**Conclusions** - In this cohort of patients who received LVADs, the rate of in-hospital mortality after OHT was lower for patients who underwent late OHT (greater than 8 days from LVAD implantation) when compared to patients who underwent OHT within 1 week of LVAD implantation, and a longer wait for OHT after LVAD placement did not correlate with longer hospital stays post OHT.

**Introduction**

Heart failure (HF) affects an estimated 5.8 million people in the United States and contributes to over 300,000 deaths every year1,2. It is the most common cause of hospital admission and readmission in people aged >65 years, annually accounting for over 2.4 million hospitalizations2,3 and $39 billion in healthcare costs1,4. Although most patients respond favorably to standard medical treatment, a considerable number of patients progress to end-stage heart failure refractory to medical therapy5. Currently, orthotopic heart transplant (OHT) is the gold standard therapy for these patients6,7,8, however the number of donor hearts available for transplantation is far fewer than the number of patients with end-stage heart failure. With the growing elderly population and improved medical treatment of HF, the proportion of end-stage heart failure patients in the United States is steadily rising and LVADs are becoming increasingly important in their care and management5.  
 The REMATCH trial in 2001 showed significant mortality reductions in patients placed on a pulsatile-flow LVAD compared to standard medical treatment9. Several subsequent studies since confirmed the survival benefit of both the older pulsatile and newer continuous-flow LVADs10-13. Patients bridged to OHT with a LVAD achieve equal survival rates as patients who undergo direct heart transplant14. Although LVADs have substantially reduced mortality in end-stage heart failure patients, the absolute mortality rates still remain high. A large portion of this mortality is attributable to complications and other occurrences during the patient’s stay in the hospital15. In-hospital mortality rates as high as 27% have been reported in patients after LVAD surgery15. As the rate of LVAD implantation in the United States increases19-22, effective recommendations on the in-hospital management of LVAD implantation are essential.

Past studies on the appropriate use and outcomes of LVADs have been mostly limited to institutional experience and case series of select populations. While such descriptive investigations are useful, they are often limited by small sample size and variation between institutions and comparison groups. Therefore, here we use the National Inpatient Sample, the largest national database of hospitalizations in the United States with data from over 36 million hospitalizations, to assess the optimal management of patients before, during, and after LVAD implantation in the hospital. In particular, we report trends in mortality by duration of hemodynamic monitoring, timing of LVAD implantation, and wait time for same-admission OHT. We also report trends in LVAD mortality by age, gender, and year and present demographic characteristics of documented LVAD recipients from 1998 to 2011.

**Methods**

**Data Source**

The Nationwide Inpatient Sample (NIS), from the Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality, is the largest database of all-payer inpatient discharge information, sampling approximately 20% of all non-federal US hospitals and including approximately 9 million hospital admissions each year. It contains discharge data from over 5000 hospitals located across 45 states, of which approximately 1,200 hospitals are sampled each year to create a stratified sample of United States hospitals. Each NIS entry includes all diagnosis and procedure codes of activity during the patient’s hospitalization at the time of discharge, as well as patient demographics, hospital characteristics, and short-term complications of the hospitalization.

**Study design and Cohorts**

This was a retrospective cross-sectional study using the Nationwide Inpatient Sample (NIS) between 1988 and 2011. We identified all hospitalizations from 1988 to 2011 of patients 18 years of age or greater that underwent placement of a left ventricular assist device and for which the hospital day of each procedure was available. Procedures during the hospitalization in addition to LVAD placement, including orthologous heart transplant, extracorporeal membrane oxygenation, intubation, hemodialysis, invasive hemodynamic monitoring, and surgical revision were identified by associated ICD9 codes (Supplementary Table A). Additionally, hospital mortality and perioperative morbidity such as post-operative infections, cardiopulmonary complications, and hemorrhagic complications requiring endoscopy were identified.

**Statistical Analysis**

Python 2.7 (Python Software Foundation, www.python.org) and R 2.13 (R Foundation, www.r-project.org) were used for statistical analysis. P-values for numerical and count data was calculated by two-sided t-tests and Chi-squared tests, respectively, with significance thresholds of 0.05.

**Results**

**Baseline Patient Characteristics**

We identified 2200 patients greater than 18 years of age in the National Inpatient between 1998 and 2011 who underwent LVAD implantation and for which hospital day of procedure was listed (Table 1). The mean age of all patients was 53.4 years (SD = 13.7, range = 18-92 years).The mean day of LVAD implantation was 9.4days (SD = 12.5 days) into the hospitalization. Patients who underwent LVAD implantation on the first or second day of hospitalization had increased mortality (33.4% vs. 24.3%, p = 0.001). The overall in-hospital mortality rate was 26.8%, with an age-associated relationship to mortality (R2 = 0.632, 3.4% increase in mortality per decade of life, p = 0.001). More male patients received LVAD implantations than female patients [n = 1659 (75.4%) vs. n = 541 (24.6%)], and in-hospital mortality rates were higher among females than males (32.0% vs 24.7%, p = 0.001). Whites patients comprised the largest proportion of LVAD recipients (57.9%), followed by Black patients as the second largest racial group(16.0%), and in-hospital mortality rates was significantly lower in Black patients(18.1% vs. 28.4%, p < 0.001).

Most LVAD implantations were performed in large(87.8%), urban (99.1%), teaching hospitals (92.4%). Mortality rates were higher in patients who received LVAD implantations in small (n = 38, 50.0%, p < 0.001), rural (n = 19, 52.9%, p < 0.001), and non-teaching hospitals (n = 165, 37.6%, p < 0.001). Temporal trends in LVAD showed an increase in the number of implantations from 1998 to 2011 (r^2 =0.6924, trend p-value <0.001). Overall in-hospital mortality remained stable between 1998 and 2006 (r^ 2 = 0.1403, trend p-value = 0.9042) and linearly decreased between 2007 and 2011 (r^2 = 0.7648, trend p value = 0.033) (Figure 1).

**Comorbidities and Complications**

The most common comorbidities observed in patients were diabetes (17.8%), disorders of lipid metabolism (14.1%), hypertension (13.7%), history of or current use of tobacco (6.5%) , and BMI ≥ 30 kg/m2 (4.4%). Respiratory failure, cardiac dysrhythmias, right heart failure, and renal failure are among the most frequent in-hospital complications immediately following LVAD implantation (Table 2). Of the 2200 patients, 2130 received one LVAD, 67 received two LVADs, and 3 received three LVADs during the same admission. Repeat LVAD surgeries suggest significant surgical complications, with significant excess mortality in patients who received two LVADs (56.7%) and three LVADs (100.0%).

**Timing of Post-LVAD Orthologous Heart Transplant**

Of these patients who underwent LVAD implantation, 164 (7.5%) patients also underwent orthologous heart transplant during the same hospitalization (Figure 3). OHT occurred a median of 32 days (IQR 7.75 to 66 days) after LVAD implantation (Table 3). Of patients who underwent OHT, increased in-hospital mortality was identified in patients who underwent transplantation within 7 days of LVAD implantation compared to patients who underwent transplant after 8 days (26.8% vs. 12.2%, p = 0.0483). There was no statistically significant difference in patient demographics with regards to age, sex, race, household income, or number of comorbid diagnoses. Patients who waited longer after LVAD implantation for OHT had longer hospital stays (39.3 ± 33.2 days for the first quartile, 48.87 ± 25.6 days for the second quartile, 85.8 ± 40.1 days for the third quartile, 151.2 ± 52.6 days for the fourth quartile). Compared to patients who underwent LVAD implantation but did not undergo OHT, patients who underwent late OHT after LVAD had decreased mortality (12.2% vs. 27.0% p < 0.001). Patients who underwent early transplant after LVAD did not show a similar mortality benefit (26.8% vs. 27.0%, p = 0.946).

**Discussion:**

In this study, we identified two thousand two hundred patients in the Nationwide Inpatient Sample between 1998 and 2011 who underwent LVAD implantation, of which 432 underwent pre-procedural invasive hemodynamic monitoring and 164 underwent orthologous heart transplant in the same hospitalization. This is the largest analysis of the timing of invasive hemodynamic monitoring, LVAD implantations and post-LVAD OHT surgeries, with data from 211 hospitals in the United States represented. We found patients with invasive hemodynamic monitoring had increased in-hospital survival (80.1% vs 71.9%, p<0.001) despite longer hospitalizations and longer time to LVAD implantation during the hospitalization. Patients who underwent LVAD implantation within 48 hours of admission had worse survival (66.6% vs. 75.7%, p = 0.001). For patients who also underwent OHT during the same hospitalization, mortality was decreased for patients who underwent OHT greater than 8 days after LVAD implantation compared to both patients who did not receive OHT and patients who underwent OHT within 1 week of LVAD implantation (12.2% vs. 26.8%, p = 0.0483).

Between 1998 and 2011, that has been a significant increase in the number of LVAD implantations however the characteristics of this population - including timing of LVAD, usage of invasive hemodynamic monitoring, and timing of post-LVAD OHT - has remained relatively unchanged. Our data is consistent with previous smaller studies using other databases with regard to age, gender, race, and other demographic characteristics. Our survival results are similar to multiple prior studies suggesting a downward trend in in-hospital mortality after 2005. The optimal management and timing of LVAD implantation is still mostly dependent on institutional experience and provider preference as there are no randomized control trials due to the relatively novel introduction of LVADs and small patient populations.

The use of invasive hemodynamic monitoring is controversial but can provide additional information on the clinical status of end-stage heart failure patients and help optimize volume status and cardiac output. Our data suggests that patient who underwent invasive hemodynamic monitoring had increased hospital survival compared to patients who did not have invasive hemodynamic monitoring (80.1% vs 71.9%, p<0.001). This difference in survival is robust despite patients with invasive hemodynamic monitoring having longer time to LVAD implantation (13.4 days vs. 8.5 days, p < 0.001) and longer hospital stays (45.4 days vs. 39.3 days, p = 0.003). On subset analysis, it appears that patients who had invasive hemodynamic monitoring the longest had the greatest mortality benefit compared to patients without invasive hemodynamic monitoring (Supplementary Figure C). Patients who underwent LVAD implantation within 48 hours of admission had worse survival (66.6% vs. 75.7%, p = 0.001), suggesting urgent or emergent surgery in the setting of acute decompensation leads to worse surgical outcomes. Consistent with our data on invasive hemodynamic support, this suggests optimal medical management of volume status and clinical status prior to surgery could lead to improved survival.

For patients who receive an LVAD for bridge to transplant therapy (BTT), the optimal timing of post-LVAD OHT is controversial. The need for clinical stability and time to recover from major surgery is balanced by the risk of LVAD complications and the formation of adhesions and scarring in determining the optimal time for OHT after LVAD. In our study, patients who underwent post-LVAD OHT had decreased in-hospital mortality compared to patients who underwent LVAD alone (19.8% vs. 27.0%, p = 0.024), however this mortality benefit was not seen in patients who underwent early (within 7 days of LVAD implantation) orthologous heart transplant (26.8% vs. 27.0%, p = 0.946).Patients who undergo post-LVAD transplant after 7 days had much less inpatient mortality (Figure 2). This is consistent with changes in UNOS allocation system as it was thought that the October 1999 UNOS allocation system considering LVAD patients within 30 days of implant to be status 1A lead to poor outcomes of transplant surgeries soon after LVAD implant. Our data suggesting early post-LVAD transplant can lead to inferior outcomes is consistent with other retrospective data suggesting the optimal time interval to be between 1 and 3 months after implantation.

Our study has a few limitations. First, the NIS is a deidentified administrative database dependent on the appropriate coding of individual ICD-9-CM codes. Studies using such databases are susceptible to errors related to coding such as undercoding complications or variation in the application of diagnostic codes. This database also lack many details available in registries and unmeasured confounders cannot be excluded. Additionally, the NIS only captures events during the hospitalization, so complications and adverse events after discharge are not recorded. This limitation is counterbalanced by the larger sample size and the absence of reporting bias introduced by the publication of institutional experiences from a few specialized centers. Additionally, patients who underwent LVAD implantation have long hospital stays that capture most, if not many, of the acute complications causing morbidity and mortality. Studies have shown excellent long-term outcomes in LVAD patients who have uncomplicated hospital courses past 30 days.

In conclusion, our analysis demonstrates that the use of LVAD has increased significantly between 1998 and 2011 while simultaneously decreasing complication and mortality rates. The use of pre-procedure invasive hemodynamic monitoring appear to decrease in-hospital mortality, independent of age, sex, race, income, and comorbidities. Early LVAD implantation during the hospitalization and early post-LVAD OHT are associated with excess mortality. Increased understanding of the characteristics, management, and timing of LVAD implantation and post-LVAD transplant can improve future outcomes.

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