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In-hospital outcomes of a minimally invasive off-pump left thoracotomy approach using a centrifugal continuous-flow left ventricular assist device

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KEYWORDS:
left thoracotomy;
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surgical approach

BACKGROUND: Minimally invasive left thoracotomy (MILT) and off-pump implantation strategies have been anecdotally reported for implantation of the HeartWare ventricular assist device (HVAD). We analyzed our experience with off-pump MILT implantation techniques and compared early in-hospital outcomes with conventional on-pump sternotomy (CS) implantation strategy.

METHODS: Between January 2013 and February 2014, 51 patients underwent HVAD implantation and were included in this study. Thirty-three patients had CS, whereas 18 patients underwent off-pump MILT. To compare outcomes of these techniques, a multivariate analysis using propensity score modeling was performed after adjusting for age, INTERMACS, Kormos and Leitz-Miller (LM) scores.

RESULTS: Mean age at implant was 57 (range 18 to 69) years, and overall in-hospital mortality was 8%. Univariate analysis revealed a statistically significant reduction in days on inotropes ($p = 0.04$), and a trend toward reduced intra-operative blood product administration ($p = 0.08$) in the MILT group. There was no difference in intensive-care-unit length of stay ($p = 0.5$), total length of stay ($p = 0.76$), post-operative blood product administration ($p = 0.34$) and total time on mechanical ventilation ($p = 0.32$). After adjusting for age, INTERMACS profile and Kormos and LM scores, no statistically significant differences were observed between the MILT and CS groups.

CONCLUSIONS: An off-pump MILT implantation strategy can be utilized as a safe surgical approach for patients undergoing HVAD implantation. Further large collaborative studies are needed to identify advantages of the MILT approach.

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Left ventricular assist device (LVAD) therapy has been demonstrated to be an effective strategy to bridge patients with decompensated heart failure to transplantation.[1] Over the past decade, advances in LVAD pump technology,

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combined with a better understanding of patient management, have allowed constant improvements in outcomes and long-term durability after implantation.[2] Circulatory support using the centrifugal continuous-flow HeartWare ventricular assist device (HVAD; HeartWare International, Inc., Framingham, MA) has become an established and effective strategy to bridge patients to heart transplantation.[3] The smaller pump design and intra-pericardial placement of the HVAD has allowed for the development of alternative and less invasive implantation techniques.[4–6]

Less invasive interventions for patients with advanced heart failure requiring mechanical circulatory support represent a paradigm shift for this challenging patient population. Several newer approaches have been decribed for insertion of devices.[7] Through miniaturization of the HVAD system, case reports or small series of successful off-pump implants and less invasive alternative approaches have been published.[5,8] Despite the theoretical advantages of these proposed surgical implant strategies, comparisons with a conventional on-pump sternotomy strategy need to be determined.

We conducted this study to compare two surgical HVAD implant strategies and also evaluated the impact of surgical technique on early peri-operative and in-hospital outcomes. The primary objective of this study was to compare results of a conventional on-pump sternotomy (CS) technique versus a relatively newer off-pump, minimally invasive left thoracotomy (MILT) approach.

Methods

Study design

Our investigation was a retrospective analysis of prospectively gathered data from January 2013 to February 2014. The study was approved by the institutional review board of the Vanderbilt University Medical Center. Patients were invividually consented for the surgical approach utilized and agreed to move forward with the proposed implant technique despite the investigational nature of the off-pump left thoracotomy strategy. For all patients in the conventional surgery group (CS group), a conventional on-pump technique with standard mid-line sternotomy was utilized for HVAD implantation, whereas patients in the second group had the implant performed through an off-pump left thoracotomy approach (MILT group).

Upon approval by the LVAD multidiciplinary selection committee, all patients were evaluated to proceed to implant using a less invasive surgical implantation technique. During our evaluation process, to select the appropriate implant strategy, we reviewed baseline pulmonary function testing and the non-contrast chest computed tomography to determine the physiologic and anatomic risks associated with a left thoracotomy and anatomic positioning of the ascending aorta. For patients with chronic obstructive lung disease, careful evaluation of the capacity for post-operative pulmonary recovery from a thoracotomy was assessed. In patients with multiple previous proximal bypasses, the length of the ascending aorta was combined with patency of grafts on pre-operative angiogram and balanced with challenges of a less invasive approach for ascending aortic outflow graft anastomosis. Patients were excluded from this study if they required concomitant surgery for left ventricular or left atrial appendage clot, significant aortic insufficiency, mitral stenosis, severe tricuspid regurgitation and patent foramen ovale.

Eighty-five patients were implanted with a long-term continuous-flow LVAD from January 2013 to February 2014. Of these, 51 patients who consented to the Advanced Heart Failure Registry were included in the final analysis. Patients with biventricular HVAD implantation were excluded. Baseline and peri-operative data were collected and compared between groups for peri-operative and in-hospital outcomes. Patients were followed systematically through discharge for the purpose of this study, and clinical follow-up was 100% complete.

Pre-operative anti-coagulation

The elective nature of the interventions allowed management of pre-operative anti-coagulation and anti-platelet medications before device implantation. Both clopidogrel and warfarin were held 5 to 7 days before the operation, whereas aspirin was preferentially held on the day of the intervention. Pre-operative bridging using a heparin drip was only used on patients withdrawn from warfarin who had mechanical valves. All post-operative anti-coagulation and anti-platelet therapy was protocol driven: aspirin 325 mg (enteric-coated) was given daily starting on post-operative day (POD) 1, whereas coumadin (international normalized ratio [INR] goal 2.0 to 3.0) was initiated beginning on POD 2. Post-operative heparin infusions are not used routinely at our center unless the INR goal is not reached before POD 5.

Blood product administration

Blood products were given to patients during the intra- and peri-operative time periods in accordance with blood conservation guidelines of the Society of Thoracic Surgeons.[9] Based on evaluation of bleeding diathesis throughout the intervention, the implanting surgeon (same surgeon throughout study duration) or the anesthesiologist worked together conjointly to implement these guidelines. Post-operatively, the intensive-care-unit (ICU) physician participated in the transfusion decision if active coagulopathic state was suspected. Fresh frozen plasma or cryoprecipitate was utilized when a coagulopathy was identified, whereas platelets were given when the platelet count was $<50{,}000$ and there was evidence of active bleeding.

Surgical techniques

Left thoracotomy implantation

For the patients included in the MILT group, a less invasive modified approach, as described by Schmitto et al,[5] was used, with modifications made for off-pump placement. A 6-cm left anterior thoracotomy was combined with a 4-cm upper hemi-sternotomy for outflow graft placement. A modified non-fibrillatory technique was used for inflow cannula placement. After setting the permanent pacemaker to a backup rate of 40 beats/min, a 30-mg bolus of adenosine was given to induce brief asystole, during which the LV apex was quickly incised to secure the LV coring tool. After a brief recovery period, a similar second bolus of adenosine was given to complete LV coring and lock the HVAD to its final position. The ouflow graft was tunneled within the pericardium and anastomosed end-to-side to the proximal ascending aorta. De-airing was accomplished by first filling the outflow graft with saline to

minimize air burden in the system. During insertion of the inflow cannula, the outflow cannula was left unclamped for the first couple of beats, as the LV would start to eject after recovery from adenosine-induced aystole. This maneuver is critical in de-airing of the inflow cannula and LVAD. Transesophageal echo is concomitantly used during this maneuver to monitor any evidence of residual air in the LV. With the aforementioned maneuver, we have been able to eliminate air burden in the LV after insertion of the inflow cannula. De-airing of the outflow cannula was achieved by placing a de-airing needle in the outflow cannula in a standard fashion, before unclamping the aortic partial clamp. Before removing the partial occluding clamp, the HVAD was initiated at 1,800 rpm and the outflow graft was de-aired through the aortic anastomosis.

Conventional sternotomy implantation

For patients in the CS group, a standard implantation technique was utilized for pump implant as described previously by Slaughter et al.[10] A mid-line sternotomy was used for mediastinal access and initiation of cardiopulmonary bypass (CPB). Inflow ring implantation, coring of the LV apex, and subsequent outflow graft anastomosis using a partial cross-clamp were performed using a standard on-pump approach. De-airing was accomplished by insertion of a root vent and through a small de-airing hole in the outflow graft. Transesophageal echo was utilized to determine the presence of air in the LV during separation from CPB. Weaning from CPB and initiation of HVAD was completed after confirmation of absence of LV air was done.

Statistical analysis

Mean and standard deviation were calculated for continuous variables. Pearson's test was used to calculate *p*-values for binomial variables, whereas Wilcoxon's test was used for continuous variables. Logistic regression models were fitted on surgical techniques for in-hospital-death, and linear regression models were fitted for other outcomes. Age, INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) profile and Leitz-Miller (LM) and Kormos scores were propensity adjusted. Propensity scores were included in the model as a single covariate and the interaction between surgical technique and propensity score was found to be non-significant and therefore not included in the final model. The mean outcome for each surgical technique and the mean difference the outcome between two techniques were estimated for an "average" subject, with propensity scores equal to its mean value. The corresponding confidence intervals were constructed based on the normality assumption in the linear model and Wald's statistics and the delta method in the logistic regression model. When the 95% confidence interval of the estimated difference was within the equivalence region, the null hypothesis was rejected and equivalence between the two surgical techniques was reached.

Results

Between January 2013 and February 2014, 51 patients were found to meet our study inclusion criteria and underwent HVAD implantation. Thirty-three patients (26 men, or 79%) had a CS implant, whereas 18 (12 men, or 72%) were approached using a MILT. All patients were implanted for a bridge-to-transplantation indication. Median age at implant was 57 (range 18 to 69) years. The two groups were similar in pre-operative characteristics, including INTERMACS profile and Kormos and LM scores (Table 1).

Post-operatively, there were 4 in-hospital deaths (8%) reported for the entire population, all occurring in the CS group. Four patients had stroke, including 3 (9%) in the CS group and 1 (6%) in the MILT group. Mean ICU length of stay for all patients was 6.5 ± 4.7 days, whereas total in-hospital length of stay averaged 13.5 ± 6.2 days. Intra-operative blood product administered averaged 6.1 ± 11.1 units, whereas post-operative transfusions averaged 2.7 ± 7.1 units. Patients were on inotropic support for an average of 5.9 ± 4.3 days, and on mechanical ventilation for an average of 1.4 ± 2.3 days.

Early comparative outcomes

A statistically significant decrease in post-operative days on inotropes was seen in the MILT group as compared with the

Table 1 Patients' Demographics

	Overall group	Conventional sternotomy	MILT	*p*-value
Number	51	33	18	
Age (years)	53 ± 12[a]	52 ± 12	55 ± 12	0.39[a]
Female gender (%)	24% ($n = 12$)	21% ($n = 7$)	28% ($n = 5$)	0.85[b]
Ischemic heart failure (%)	53% ($n = 27$)	55% ($n = 18$)	50% ($n = 9$)	0.78[b]
Pre-operative IABP (%)	16% ($n = 8$)	24% ($n = 8$)	0% ($n = 0$)	0.04[b]
Redo sternotomy (%)	29% ($n =15$)	30% ($n = 10$)	28% ($n = 5$)	0.85[b]
Diabetes (%)	24% ($n = 13$)	24% ($n = 8$)	28% ($n = 5$)	0.78[b]
Pre-operative moderate/severe RV dysfunction (%)	30% ($n = 15$)	31% ($n = 11$)	22% ($n = 4$)	0.61[b]
INTERMACS score	3.1 ± 1.2	3.0 ± 1.1	3.3 ± 1.4	0.75[a]
Kormos score	0.47 ± 0.22	0.44 ± 0.24	0.52 ± 0.17	0.13[a]
LM score	8.2 ± 5.6	8.8 ± 5.4	6.9 ± 6.0	0.27[a]
LVEF	17.8 ± 7.2	17.2 ± 7.9	18.2 ± 5.5	0.47[a]
Pre-operative creatinine	1.45 ± 0.88	1.35 ± 0.34	1.58 ± 1.41	0.49[a]
Preoperative bilirubin	1.2 ± 0.8	1.3 ± 0.9	0.9 ± 0.6	0.15[a]

Data presented as mean ± 1 standard deviation. IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; LM, Leitz-Miller; MILT, minimally invasive left thoracotomy, RV, right ventricle.

[a]Wilcoxon's test

[b]Pearson's test.

Table 2 Univariate Outcomes Comparison Between Minimally Invasive Left Thoracotomy and Conventional Sternotomy

Outcome	Conventional sternotomy (CS)	Left thoractomy (MILT)	*p*-value
In-hospital mortality	4 (12.1%)	0 (0.0%)	
ICU LOS (days)	3.0, 5.0, 7.0 (6.5 ± 5.4)	4.0, 6.0, 8.0 (6.4 ± 3.7)	0.5
Total LOS (days)	9.0, 12.0, 16.5 (13.7 ± 6.1)	10.2, 12.5, 17.0 (13.2 ± 3.8)	0.76
Total BP received in OR	0.0, 2.0, 7.0 (8.3 ± 13.0)	0.0, 1.0, 2.0 (1.9 ± 4.1)	0.08
Total BP post-operatively	0.0, 0.5, 3.0 (3.5 ± 8.7)	0.0, 0.0, 1.8 (1.3 ± 2.5)	0.34
Time on inotropes (days)	3.5, 6.0, 8.5 (6.6 ± 3.8)	1.2, 3.5, 5.8 (4.7 ± 4.8)	0.04[a]
Time on MV (days)	0.0, 1.0, 1.5 (1.2 ± 1.1)	0.0, 0.0, 1.8 (1.6 ± 3.4)	0.32

Data presented as number (%) for in-hospital mortality, and as lower quartile, median, upper quartile (mean ± 1 standard deviation) for the remaining data. BP, blood product; CI, confidence interval; CS, conventional sternotomy; ICU, intensive care unit; LOS, length of stay; MILT, minimally invasive left thoracotomy; MV, mechanical ventilation; OR, operating room.

[a] $p < 0.05$ (statistically significant).

CS group (mean 4.7 ± 4.8 vs 6.6 ± 3.8, $p = 0.04$). ICU length of stay and total in-hospital length of stay was similar between the two groups (Table 2). Intra-operative blood product requirement for MILT patients averaged 1.9 ± 4.1 units compared with 8.3 ± 13.0 units for the CS group ($p = 0.08$). Post-operatively, the MILT group received an average of 1.3 ± 2.5 units, whereas the CS group received 3.5 ± 8.7 units ($p = 0.34$) (Table 2). Propensity score multivariate analysis revealed comparable early outcomes between groups (Table 3).

Discussion

Ventricular assist device surgery has become an integral procedure for the treatment of terminal heart failure.[11] HVADs, approved by the U.S. Food and Drug Administration in November 2012 for bridge-to-transplant indications, have been used with greater frequency, with more than 2,500 pumps placed worldwide.[12] The surgical approach for HVAD placement has tradionally been a mid-line sternotomy using CPB.[10] Although this approach has been successful, it may increase the risk of post-operative bleeding[13] and infection,[5,14–17] and may also be associated with increased risk of complications from redo sternotomy in patients bridged to transplantation. Furthermore, opening the pericardium in patients undergoing LVAD implant may be associated with increased risk of right ventricular (RV) dilation from alteration of the RV pressure-volume relationship.[18] Less invasive surgical approaches were developed with the hopes of reducing CPB time and operative trauma, minimizing peri-operative blood loss, protecting cardiac structures from multiple re-entries, and preserving heart geometry.[19] Haberl et al recently described their surgical techniques and clinical experience in minimally invasive implant strategies for HVAD and HeartMate II.[20] Of the 27 patients in their study, 5 (19%) were done off-pump. They had a reported in-hospital mortality of 14.8%, and average hospital stay of 30 days. Based on their findings, they concluded that minimally invasive LVAD implantation is feasible and safe.

Main findings of this study

To our knowledge, this is the first work describing a comparison of short-term in-hospital outcomes between a conventional sternotomy versus a minimally invasive left thoracotomy off-pump approach for HVAD implantation. Our results show that patients who underwent on-pump conventional sternotomy had a significantly longer duration of inotropes compared with the off-pump MILT group. This could be secondary to better intra-operative protection of the RV by avoiding CPB and mid-line sternotomy. The remainder of early peri-operative and in-hospital outcomes between the MILT and the CS groups were comparable.

Potential implications of a less invasive strategy

Minimally invasive approaches to cardiac surgery have been used in mitral and aortic valve procedures in the past, with comparable or improved outcomes to conventional approaches.[19] Similar mortality rate,[21] shorter ICU/hospital

Table 3 Propensity Score Adjusted Comparison Between Off-pump Minimally Invasive Left Thoractomy and On-pump Conventional Sternotomy Techniques

Outcome	MILT estimate	CS estimate	Difference MILT-CS [95% CI]	*p*-value
In-hospital mortality	0	0.117	−0.117 [−0.001, 0.235]	0.05
ICU LOS (days)	6.3	6.58	−0.28 [−3.37, 2.81]	0.86
Total LOS (days)	13.3	13.63	−0.33 [−3.75, 3.09]	0.85
Total BP received in OR	2.67	7.91	−5.24 [−11.83, 1.36]	0.117
Total BP post-operatively	0.83	3.83	−3.00 [−7.44, 1.43]	0.18
Time on inotropes (days)	4.72	6.60	−1.88 [−4.53, 0.77]	0.16
Time on MV (days)	1.76	1.07	0.69 [−0.80, 2.18]	0.35

BP, blood product; CI, confidence interval; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; OR, operating room.

stay,[22] overall lower costs,[23] decreased post-operative bleeding[13,24] and improved cosmesis[25] have been shown to be some of the benefits of a less invasive surgical strategy. It is concievable that some of these advantages could be obtained for MILT LVAD surgery. In patients with prior sternotomy, the use of a MILT approach can potentially minimize trauma associated with obtaining access to the LV. In bridge-to-transplant candidates, avoiding a full sternotomy during LVAD implantation may make subsequent LVAD explantation and heart transplantation technically less challenging by minimizing adhesions and allowing easier identification of dissection planes.

Disadvantages of a less invasive strategy need to be aknowledged. Given that thoracotomy incisions are small, direct access of the LV apex could be technically more challenging and may result in improper placement of the inflow cannula. We found the use of intra-operative transthoracic echocardiography to identify the LV apex before performing the left thoracotomy can assist the surgeon in identifying the ideal position for the thoracotomy incision. A hemi-sternotomy incision also results in limited exposure of the ascending aorta and can be technically challenging, especially if an emergent need to go on CPB develops.

Activation of the systemic inflammatory response due to CPB and associated deleterious effects on the coagulation system have been well documented in the literature.[26] Fibrinolysis, platelet sequestration and degradation of coagulation factors are some of the negative effects of the CPB machine.[27–29] Although the long-term benefits of off-pump vs on-pump coronary artery bypass surgery are controversial, the short-term benefits of off-pump surgery to reduce the rates of blood product transfusion, reoperation for peri-operative bleeding, acute kidney injury and respiratory complications have been demonstrated in large studies.[30] Minimizing blood product transfusion and reducing exposure to blood antigens decreases the risk of allosensitization, thus preserving donor pool availability for bridged candidates undergoing HVAD implantation.[31] Our choice of a minimally invasive left thoractomy and off-pump implantation strategy was an attempt to minimize the potential complications from mid-line sternotomy and CPB.

Technical considerations

Although rapid ventricular pacing has been described to reduce LV ejection in other procedures, our technique involves the use of an adenosine-induced asystole for off-pump placement of the HVAD. Adenosine-induced asystole renders the LV immobile, making it easy for the surgeon to the place inflow cannula in the LV at a precise moment and position. In addition, because of adenosine-mediated pulmonary vasodilation, pulmonary artery pressure is minimized, which may protect the RV.[32,33] Last, adenosine has an extremely short half-life, which minimizes the deleterious effects of rapid pacing–induced asystole.[34,35] Because most heart failure patients have permanent pacemakers, it is important to set a low back-up rate pre-operatively to achieve desired bradycardia intra-operatively.

Limitations

There are several limitations to our study. This is a retrospective analysis of prospectively collected data, and is therefore it is subject to the limitations associated with retrospective studies. End-organ function is routinely optimized using an intra-aortic balloon pump (IABP) before the intervention, and difference in IABP utilization between groups is not a marker of sickness in this patient population. Comparison between the CS and MILT groups showed no difference in pre-operative risk status, as measured by INTERMACS profile and Kormos and LM scores. Thus, we believe the comparison between the two groups remains valid. The off-pump MILT sample size was small, which reduces the statistical power and ability to infer positive findings. It is also important to note that this study was not powered to assess mortality, so no conclusion can be made on the mortality benefit of the off-pump MILT approach. In addition, our study has evaluated a new alternative technique for HVAD placement (off-pump as well as MILT) and compared the approach to the standard of care performed through an on-pump mid-line sternotomy. As such, it will be difficult to tease out which aspect of the new technique (off-pump vs minimally invasive) contributed to reduced days on inotropes and reduced intra-operative blood product administration. In addition, peri-operative bleeding is multifactorial and unlikely due to only one peri-operative factor, especially in this complex group of patients with advanced heart failure. Investigation of different implant strategies will likely lead to a tailored surgical approach and will perhaps optimize peri-operative outcomes in patients implanted with LVAD technology. As such, larger studies need to be done to determine which approach improves these outcomes. Last, all procedures were performed at one institution and by one surgeon, and therefore generalizability may be limited and affected by surgeon experience and institutional practice. A randomized, controlled trial assessing MILT to CS is needed to further study and compare the risks and benefits of these surgical techniques.

In conclusion, the minimally invasive off-pump left thoracotomy approach is feasible and can be utilized safely as an alternative surgical strategy for HVAD implantation. Early surgical outcomes compare favorably to a conventional sternotomy approach. In addition, similar early in-hospital outcomes were achieved using an off-pump, minimally invasive approach. Less invasive approaches offer the potential of improving outcomes in high-risk surgical groups. Further larger collaborative studies are needed to detect differences and possible advantages for both implant strategies.

Disclosure statement

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