Research paper

Predictors of perioperative bleeding in left ventricular assist device implantation

Mohammed Elzeneini [a,1], Ahmad Mahmoud [b,1], Abdelrahman H. Elsayed [c], Yasmeen Taha [b], Lauren E. Meece [d], Mohammad Al-Ani [b], Eric I. Jeng [e], George J. Arnaoutakis [e], Juan R. Vilaro [b], Alex M. Parker [b], Juan Aranda Jr. [b], Mustafa M. Ahmed [b,*]

[a] Department of Internal Medicine, University of Florida, Gainesville, FL, USA
[b] Division of Cardiovascular Medicine, University of Florida, Gainesville, FL, USA
[c] Division of Pharmacotherapy & Translational Research, University of Florida, Gainesville, FL, USA
[d] Department of Surgery, University of Florida, Gainesville, FL, USA
[e] Division of Thoracic & Cardiovascular Surgery, University of Florida, Gainesville, FL, USA

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ABSTRACT

Study objective: Early bleeding is a common source of morbidity associated with left ventricular assist device (LVAD) implantation. Our objective was to identify potential predictors of peri-implant bleeding.

Methods: We conducted a retrospective cohort study of LVAD implants at our institution between January 2010 and November 2018. A total of 210 patients were included. Data were collected for the duration of implant hospitalization, including perioperative invasive hemodynamics, echocardiography and operative details, antiplatelet and anticoagulant use, bleeding events and blood product use, and thromboembolic events. Peri-operative bleeding was defined as a transfusion requirement of >4 units of packed red blood cells in the intraoperative and first 7 days postoperative period, or a major 7-day post-implant overt bleeding event requiring procedural intervention.

Results: Perioperative bleeding occurred in 32% of patients and required surgical re-exploration in 9%. Multivariable logistic regression analysis identified history of previous sternotomy (OR 2.63, 95% CI 1.29 to 5.35, p-value 0.008), preoperative glomerular filtration rate <60 ml/min (OR 2.58, 95% CI 1.34 to 4.94, *p*-value 0.004), preoperative right atrial pressure >13 mm Hg (OR 2.36, 95% CI 1.19 to 4.67, *p*-value 0.014) and concomitant tricuspid valve repair (OR 2.48, 95% CI 1.23 to 5.01, p-value 0.011) as independent predictors of perioperative bleeding. In-hospital thromboembolic events occurred in 5% of patients, but there were no significant predictors for them.

Conclusions: Elevated right atrial pressure appears to be a reversible risk factor for early bleeding that should be targeted during pre-implant optimization of LVAD candidates.

1. Introduction

Left ventricular assist device (LVAD) implantation is an established therapeutic option for patients with advanced heart failure as bridge to transplantation (BTT) or destination therapy (DT). Despite the growing use of continuous-flow LVADs (CF-LVADs), they are associated with high complication rates of bleeding and thrombosis [1,2]. Bleeding is the most common adverse event in the early postoperative period [2], and is a major source of morbidity and mortality in LVAD recipients.

Despite the presence of ample literature on risk factors of late bleeding events in LVAD recipients including gastrointestinal (GI) bleeding, there is limited literature on risk factors for early perioperative bleeding. The ENDURANCE and MOMENTUM 3 trials reported similar high rates of early bleeding events in each of the HeartMate (HM) II, HeartWare (HW) and HM III LVAD, requiring surgery in 10% to 18% of patients. Early perioperative bleeding in LVAD implantation has been linked to a worse survival rate [3,4] and a source of morbidity requiring multiple blood transfusions [5] and procedural interventions. They are also associated with prolonged hospital stay and increased health care costs [6]. Multiple blood transfusions can also increase the risk of allosensitization of circulating antibodies, leading to longer transplant waitlists and potentially increasing the risk of heart transplant graft dysfunction [7].

The aim of this study is to investigate the predictors of perioperative bleeding in LVAD implantation. The potential implications of this would be to risk stratify patients to help in candidate selection and to suggest pre-implant medical optimization strategies. For better risk stratification,

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we also sought to investigate predictors of in-hospital thromboembolic events.

2. Materials and methods

2.1. Study population

We conducted a retrospective cohort study of all advanced heart failure patients who underwent a CF-LVAD implantation at our institution (University of Florida, Gainesville, FL, USA) in the period between January 2010 and November 2018. The study protocol was approved by our local Institutional Review Board. Patients were included in the analysis if they were at least 18 years of age at time of implant and had a HM II or III (Abbott) or HW (Medtronic) LVAD implantation either as BTT or DT. Patients <18 years of age were excluded from the analysis (n = 3), as well those who had incomplete chart review data (n = 13). A total of 210 patients were included in the final cohort for analysis.

2.2. Data collection

All data were obtained from electronic medical records. Chart review was conducted to obtain patients' baseline characteristics, use of antiplatelet and anticoagulant medications, and perioperative laboratory values at the time of LVAD implantation. Preoperative right ventricular (RV) function was assessed from echocardiography. Preoperative hemodynamics were assessed from right heart catheterization, including right atrial pressure (RAP), mean pulmonary artery pressure (mPAP) and pulmonary capillary wedge pressure (PCWP). Operative reports were reviewed for cardiopulmonary bypass time and concomitant tricuspid valve repair. Bleeding events and blood product use were collected for the intraoperative and first 7 days postoperative period. Data extraction was performed by 3 reviewers (ME, AM and YT) and any differences were resolved by a senior reviewer (MMA). All study data were collected and managed using a REDCap electronic data capture tool hosted at our institution [8].

2.3. Follow-up and clinical outcomes

Patients were retrospectively followed for the duration of hospital stay. Per our institutional protocol, anticoagulant and antiplatelet agents, other than aspirin, were held for 7 days preoperatively. Patients withdrawn from warfarin were bridged using unfractionated heparin (UH), which was discontinued 6 h preoperatively. Postoperatively, UH was started on day 1 followed by introduction of aspirin and warfarin anticoagulation with target international normalized ratio (INR) of 2.0 to 3.0, followed by discontinuation of UH. Our primary outcome was perioperative bleeding, defined as transfusion of >4 units of packed red blood cells (pRBCs) in the intraoperative and first 7 days postoperative period, or a major 7-day post-implant bleeding event requiring procedural intervention. This was based on a modified definition of INTERMACS major bleeding [9]. Our secondary outcome was a composite of in-hospital thromboembolic events, including ischemic stroke, transient ischemic attack, pump thrombosis, limb ischemia and deep venous thrombosis/pulmonary embolism. Both primary and secondary outcomes were defined on a patient level basis.

2.4. Statistical analysis

For descriptive analysis, continuous variables were presented as mean ± standard deviation, and categorial variables as percentages. Logistic regression analysis was performed to evaluate all variables as predictors of perioperative bleeding. Univariate regression was initially done, followed by a series of multivariable regression models containing age, gender, history of previous sternotomy, preoperative glomerular filtration rate (GFR) <60 ml/min and preoperative INR >1.4, with addition of a single additional predictor whose univariate p-value was <0.05 in each model run. We reported the Odds ratio (OR), 95% confidence interval (CI) and p-value for each predictor, as well as a False Discovery Rate (FDR) corrected

p-value for each model. The statistical software SPSS (IBM) Version 26 for Mac, and STATA Version 16.1 were used for analysis.

3. Results

3.1. Patient baseline characteristics

Pertinent baseline characteristics of our study population are summarized in Table 1. The mean age was 55.3 years and 80% were men. LVAD types were HM II (67%), HM III (16%) and HW (17%). Slightly more

Table 1
Baseline characteristics of LVAD patients.

	N (%) or mean (±SD)
Baseline characteristics	
Age, years	55.3 ± 14.1
Male gender	169 (80%)
Etiology of cardiomyopathy	
Ischemic	84 (40%)
Non-ischemic	126 (60%)
Coronary artery disease	95 (45%)
Previous sternotomy	52 (25%)
Diabetes	85 (40%)
Hypertension	108 (51%)
BMI	29.9 ± 6.9
Mean BMI	94 (45%)
Obesity (BMI >30 kg/m^2)	3 (1%)
Underweight (BMI <18.5 kg/m^2)	
Chronic kidney disease	
Stage III–V (eGFR <60 ml/min/1.73 m^2)	107 (51%)
Stage IV or V (eGFR <30 ml/min/1.73 m^2)	12 (6%)
Chronic obstructive lung disease	18 (9%)
Preoperative echocardiography	
RV function	
Normal RV function or mild dysfunction	104 (50%)
Moderate to severe dysfunction	106 (50%)
Preoperative hemodynamics	
RAP, mm Hg	13.5 ± 6.5
PASP, mm Hg	54.2 ± 14.1
PADP, mm Hg	27.6 ± 8.2
mPAP, mm Hg	37.6 ± 9.7
PCWP, mm Hg	26.8 ± 8.8
Use of mechanical circulatory support	
Intra-aortic balloon pump	42 (20%)
Impella	2 (1%)
ECMO	3 (1%)
Preoperative serum laboratory values	
Creatinine, mg/dl	1.3 ± 0.5
Total bilirubin, mg/dl	1.1 ± 1.0
Sodium, meq/l	135.4 ± 4.1
INR	1.2 ± 0.2
Hemoglobin, g/dl	11.5 ± 2.0
Platelet count, ×1000/ml	205 ± 78
Preoperative medication use	
Aspirin	130 (62%)
Aspirin use within 3 days preoperatively	113 (54%)
Heparin (held 6 h preoperatively)	89 (42%)
P2Y12 inhibitor (held 5–7 days preoperatively)	18 (9%)
Warfarin (held 5–7 days preoperatively)	79 (38%)
DOAC (held 5–7 days preoperatively)	25 (12%)
Operative details	
LVAD type	
HeartMate II	141 (67%)
HeartMate III	34 (16%)
HeartWare	35 (17%)
Concomitant tricuspid valve repair	52 (25%)
Cardiopulmonary bypass time, min	77.0 ± 32.2

LVAD: left ventricular assist device, BMI: body mass index, RHC: right heart catheterization, RV: right ventricle, RAP: right atrial pressure, PASP: pulmonary artery systolic pressure, PADP: pulmonary artery diastolic pressure, mPAP: mean pulmonary artery pressure, PCWP: pulmonary capillary wedge pressure, INR: internalized normalized ratio, DOAC: direct oral anticoagulant.

than half of the LVADs were implanted as destination therapy (53%). Pre-operative mechanical circulatory support was used in 22% of cases. Operative details including concomitant tricuspid valve repair and cardiopulmonary bypass time are also included (Table 1).

3.2. Perioperative bleeding and blood product use

Perioperative bleeding, per our a priori definition, occurred in 32% of patients (n = 67). The mean number of perioperative pRBC transfusion in the intraoperative and first 7 days postoperative period was 2.6 units. Table 2 shows the perioperative utilization of each type of blood product and the mean number of utilized units. Postoperative bleeding sites were localized in 22% of patients (n = 47), and included hemothorax or surgical site bleeding (17%, n = 35), gastrointestinal bleeding (3%, n = 6) and others (3%, n = 6). Surgical exploration was required in 9% of patients (n = 20).

3.3. Predictors for perioperative bleeding

On univariate logistic regression analysis, patients who had perioperative bleeding were more likely to have a history of previous sternotomy, preoperative GFR <60 ml/min/1.73 m^2, preoperative RAP >13 mm Hg, lower preoperative hemoglobin and platelet counts, aspirin use within 3 days preoperatively and concomitant tricuspid valve repair during their LVAD implantation. The significance of each variable as a predictor of perioperative bleeding is outlined in Table 3. The cut-off of 13 mm Hg for dichotomization of RAP was based on the mean (13.5), median (13) and highest C statistic from a receiver operating characteristic curve (13.5). Our serial multivariable regression models revealed the following independent predictors of perioperative bleeding (Table 4): history of previous sternotomy (OR 2.63, 95% CI 1.29 to 5.35, p-value 0.008), preoperative GFR <60 ml/min (OR 2.58, 95% CI 1.34 to 4.94, p-value 0.004), preoperative RAP >13 mm Hg (OR 2.36, 95% CI 1.19 to 4.67, p-value 0.014) and concomitant tricuspid valve repair (OR 2.48, 95% CI 1.23 to 5.01, p-value 0.011). The FDR-adjusted p-value for these models was 0.07, suggesting a 7% chance the aforementioned low p-values are misleading.

3.4. In-hospital thromboembolic events

In-hospital thromboembolic events occurred in 10 patients (5%). These included ischemic stroke (n = 6, 3%), myocardial infarction (n = 2, 1%) and limb ischemia (n = 2, 1%). On univariate logistic regression analysis,

Table 2
Perioperative blood product use in LVAD implantation.

	Intraoperative n = 210	Postoperative[a] n = 210	Perioperative[b] n = 210
Blood product transfusion, N (%)			
Any blood product transfusion	174 (83%)	103 (49%)	185 (88%)
PRBC transfusion	93 (44%)	98 (47%)	131 (62%)
FFP transfusion	75 (36%)	26 (12%)	88 (42%)
Platelet transfusion	114 (54%)	31 (15%)	127 (60%)
Cryoprecipitate transfusion	67 (32%)	18 (9%)	76 (36%)
Cellsaver transfusion	96 (46%)	NA	NA
Number of utilized blood product units, mean ($\pm$SD)			
Number of total blood units	5.7 ± 7.0	2.0 ± 3.1	7.8 ± 8.1
Number of PRBC units	1.2 ± 1.9	1.4 ± 1.8	2.6 ± 2.9
Number of FFP units	1.1 ± 2.0	0.3 ± 0.8	1.4 ± 2.1
Number of platelet units	1.2 ± 1.5	0.3 ± 0.7	1.5 ± 1.7
Number of cryoprecipitate units	1.0 ± 2.5	0.1 ± 0.6	1.1 ± 2.6
Number of cellsaver units	1.2 ± 1.7	NA	NA

PRBC: packed red blood cell, FFP: fresh frozen plasma.
[a] Postoperative: first 7 days postoperative.
[b] Perioperative: intraoperative and first 7 days postoperative.

Table 3
Univariate logistic regression analysis for predictors of perioperative bleeding in LVAD implantation.

	Perioperative bleeding		
	OR	95% CI	p-Value
Baseline characteristics			
Age	1.01	0.99–1.04	0.074
Female gender	0.74	0.35–1.58	0.438
Ischemic etiology	1.34	0.74–2.41	0.334
Coronary artery disease	1.65	0.92–2.97	0.103
Previous sternotomy	3.19	1.66–6.11	<0.001
Diabetes	1.08	0.60–1.95	0.790
Hypertension	1.37	0.76–2.45	0.295
Obesity (BMI >30 kg/m^2)	1.16	0.64–2.09	0.625
Low BMI <18.5 kg/m^2	1.10	0.10–12.37	0.938
eGFR <60 ml/min/1.73 m^2	2.43	1.33–4.44	0.004
Chronic obstructive lung disease	0.40	0.11–1.43	0.190
Preoperative echocardiography			
Moderate-to-severe RV dysfunction	0.85	0.45–1.59	0.613
Preoperative hemodynamics			
RAP >13 mm Hg	2.11	1.14–3.91	0.018
mPAP (mm Hg)	0.99	0.95–1.02	0.399
PCWP (mm Hg)	1.01	0.97–1.05	0.578
Use of mechanical circulatory support	1.13	0.57–2.26	0.721
Preoperative serum laboratory values			
Total bilirubin, mg/dl	1.25	0.94–1.68	0.124
Sodium, meq/l	0.94	0.88–1.01	0.120
INR >1.4	2.20	0.79–5.92	0.080
Hemoglobin, g/dl	0.82	0.69–0.98	0.025
Platelet count/ml	0.99	0.99–1.00	0.003
Preoperative medication use			
Aspirin use within 3 days preoperatively	2.05	1.12–3.74	0.026
Heparin (held 6 h preoperatively)	1.38	0.77–2.48	0.281
P2Y12 inhibitor (held 5–7 days preoperatively)	1.07	0.38–3.00	0.892
Warfarin (held 5–7 days preoperatively)	1.18	0.65–2.14	0.583
DOAC (held 5–7 days preoperatively)	1.00	0.41–2.46	0.991
Operative details			
HeartMate III or HeartWare LVAD	0.79	0.42–1.48	0.464
Tricuspid valve repair	2.29	1.20–4.38	0.016
Cardiopulmonary bypass time > 60 min	1.80	0.80–4.05	0.158

LVAD: left ventricular assist device, BMI: body mass index, eGFR: glomerular filtration rate, RV: right ventricular, RAP: right atrial pressure, mPAP: mean pulmonary artery pressure, PCWP: pulmonary capillary wedge pressure, INR: internalized normalized ratio, DOAC: direct oral anticoagulant, OR: odds ratio.

there was no association between any of the preoperative variables and in-hospital thromboembolic events.

4. Discussion

This study investigates the incidence and predictors of perioperative bleeding in LVAD implantation in a single institutional cohort of CF-LVAD patients. Our analysis showed (i) the incidence of perioperative bleeding defined as transfusion of >4 units of pRBCs in the intraoperative and first 7 days postoperative period, or a major 7-day post-implant bleeding event requiring procedural intervention was 32%; (ii) the incidence of bleeding requiring surgical re-exploration was 9% (iii) independent predictors for the occurrence of perioperative bleeding were history of previous sternotomy, preoperative GFR <60 ml/min, preoperative RAP >13 mm Hg and concomitant tricuspid valve repair; (iv) the incidence of in-hospital thromboembolic events was 5% and there were no identifiable predictors for it.

The importance of our study findings comes from the source of morbidity and mortality of perioperative bleeding in LVAD implantation [3,4], and the sparse literature on its predictors and potential reversible risk factors. Our incidence of perioperative bleeding and surgical re-exploration rate is comparable to a recent similar single-center study [10], as well as reported rates in the ENDURANCE and MOMENTUM 3 trials [11,12]. Compared to

Table 4

Predictors of perioperative bleeding in LVAD implantation after analysis of serial multivariable logistic regression models. Each model contains age, gender, INR > 1.4, previous sternotomy, eGFR < 60 ml/min (in blue) and a single additional predictor whose univariate p-value was < 0.05.

	Perioperative bleeding				
	Univariate p-value	Multivariable OR	95% CI	Multivariable p-value	FDR-corrected p-value
Age	0.074	1.01	0.98 to 1.03	0.550	
Female gender	0.438	0.67	0.29 to 1.55	0.354	
INR >1.4	0.080	2.38	0.86 to 6.62	0.096	
Previous sternotomy	<0.001	2.63	1.29 to 5.35	**0.008**	
eGFR <60 ml/min	0.004	2.58	1.34 to 4.94	**0.004**	
RAP >13 mm Hg	0.018	2.36	1.19 to 4.67	**0.014**	**0.07**
Tricuspid valve repair	0.016	2.48	1.23 to 5.01	**0.011**	**0.07**
Aspirin use within 3 days	0.026	1.47	0.75 to 2.86	0.261	0.34
Hemoglobin, g/dl	0.025	0.83	0.69 to 0.99	0.040	0.11
Platelet count, /ml	0.003	0.99	0.99 to 1.00	0.115	0.23

LVAD: left ventricular assist device, eGFR: glomerular filtration rate, RAP: right atrial pressure, OR: odds ratio, FDR: false discovery rate.

Variables with significant p-values, or FDR-adjusted -p-values are in bold.

the axial-flow HM II LVAD, the centrifugal-flow HM III and HW LVAD were associated with similar odds of perioperative bleeding in our analysis. This similar rate of early bleeding events was also demonstrated in the ENDURANCE trial (comparing HW to HMII LVAD) [11] and the MOMENTUM 3 trial (comparing HMIII to HMII LVAD) [12] except with long-term follow-up [13].

Identification of independent predictors for perioperative bleeding can be valuable to help risk stratify patients with end-stage heart failure being evaluated for LVAD. Despite the presence of validated risk scores for perioperative bleeding in cardiac surgery [14], including the TRUST [15] and TRACK [16] scores, the LVAD population has different bleeding characteristics compared to other cardiac surgeries [17]. A preoperative predictor for the LVAD population previously suggested in the literature is ECMO use [10], in addition to reported risk factors for intraoperative blood transfusion use including urgent status, intra-aortic balloon pump use, reoperation, low body mass index and low hemoglobin [5]. Our study did not reveal an association between the use of mechanical circulatory support and perioperative bleeding, but re-demonstrated the association of re-operation/sternotomy with perioperative bleeding. Worse renal function as indicated by a pre-operative GFR < 60 ml/min was also associated with perioperative bleeding, which complements the previous literature of its association with late GI bleeding [18–20], making it a source of morbidity in LVAD recipients.

An important implication of studying perioperative bleeding is identifying potentially reversible risk factors to suggest pre-implant strategies for medical optimization. Our multivariable analysis showed that preoperative RAP >13 mm Hg increased the odds of perioperative bleeding by 2.4 times. This may be partly explained by hepatic congestion resulting in coagulopathy and/or the presence of RV dysfunction, although neither elevated INR nor RV dysfunction alone was associated with bleeding. It may also be correlated with tricuspid valve regurgitation, as tricuspid valve repair during LVAD implantation had similar odds of perioperative bleeding after multivariable analysis (in a separate model). While this study does not have the power to recommend therapeutic interventions, the results suggest that intensifying preoperative medical therapy to reduce RAP might help reduce the perioperative bleeding risk without increasing the thromboembolic risk. While this seems intuitive, there are currently no standard pre-implant strategies for medical optimization available to guide providers and an algorithm which includes pre-implant invasive hemodynamics may be of utility. Aspirin use within 3 days preoperatively is another potentially reversible risk factor that predicted bleeding on univariate but not multivariable analysis and did not predict thromboembolic events. This is important for future investigation through larger studies, as the incidence of bleeding in the early perioperative period is much higher than the incidence of thromboembolic events per the INTERMACS Database [21].

Several limitations exist in our study. First, the study had a retrospective design with reliance on chart review of electronic medical records which makes us unable to control for unidentified or unmeasured variables. It was also conducted in a single institution, with its own institutional protocol for perioperative LVAD management, which limits the ability to our findings to the general LVAD population. To address these limitations, we conducted rigorous data collection and multivariable statistical analysis with FDR correction to improve the accuracy of our findings. Furthermore, our sample included both HMII LVADs and the more contemporary HMIII and HW LVADs, although LVAD type was not associated with bleeding in our analysis. Overall, the results suggest the potential presence of reversible risk factors for perioperative bleeding, which raises the need for larger observational studies to test this hypothesis. If further supported, a prospective trial may be useful to test pre-implant medical optimization interventions for RAP to lower peri-operative bleeding risk in LVAD candidates.

5. Conclusions

Our single-center study analysis suggests that history of previous sternotomy, lower preoperative GFR, higher preoperative RAP and concomitant tricuspid valve repair are independent predictors of perioperative bleeding in LVAD implantation. If supported by future, larger studies, elevated RAP may be a reversible risk factor to be targeted during pre-implant medical optimization of LVAD candidates.

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