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Pre-Operative Right Ventricular Dysfunction Is Associated With Gastrointestinal Bleeding in Patients Supported With Continuous-Flow Left Ventricular Assist Devices

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ABSTRACT

OBJECTIVES This study sought to determine whether severe right ventricular (RV) dysfunction in the pre-operative setting is associated with an increased risk of gastrointestinal bleeding (GIB) post-left ventricular assist device (LVAD).

BACKGROUND GIB is a significant complication in patients supported with continuous-flow LVADs. The impact of RV dysfunction on the risk of GIB has not been investigated.

METHODS We retrospectively identified 212 patients who survived index hospitalization after implantation of HeartMate II (Thoratec Corp., Pleasanton, California) or Heartware HVAD (HeartWare Corp., Framingham, Massachusetts) from June 2009 to April 2013. Patients with severe RV dysfunction on pre-LVAD echocardiogram (n = 37) were compared to patients without severe RV dysfunction (n = 175). The primary outcome was freedom from GIB.

RESULTS The majority of patients were male (79%) with a median INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) profile of 2 at LVAD implantation. There were no significant differences between cohorts with respect to demographics, comorbidities, device type, international normalization ratio, or aspirin strategy. During follow-up, 81 patients had GIB events: 23 of 37 (62%) in the severe RV dysfunction group versus 58 of 175 (33%) in the control group ($p = 0.001$). After adjustment for age and ischemic cardiomyopathy, severe RV dysfunction was associated with increased risk of GIB (hazard ratio: 1.799, 95% confidence interval: 1.089 to 2.973, $p = 0.022$).

CONCLUSIONS In this single-center sample of patients supported with continuous-flow LVADs, severe RV dysfunction on pre-LVAD echocardiogram was associated with an increased risk of GIB. Further studies are needed to investigate possible mechanisms by which RV dysfunction increases the risk of GIB and to identify patient populations who may benefit from alterations in antithrombotic strategies. (J Am Coll Cardiol HF 2015;3:956–64)

Left ventricular assist devices (LVADs) have emerged as a standard of care for select patients with end-stage heart failure refractory to optimal medical therapy (1–3). Since the approval of the HeartMate II (Thoratec Corp., Pleasanton, California) in 2008, clinical experience with continuous-flow LVADs (CF-LVADs) has shown impressive and durable improvements in morbidity and mortality with survival rates of more than 80% and 70% at 1 and 2 years, respectively (1–7). Improvements in survival and quality of life measures have been shown for both bridge to transplantation (BTT)

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and destination therapy (DT) strategies (1-4,8-10). Although associated with improved outcomes, CF-LVADs have been plagued by significant long-term complications.

Complications of durable mechanical circulatory support including bleeding, infection, and thrombotic events are significant sources of morbidity in this population (1,4,7,10,11). Gastrointestinal bleeding (GIB) represents the most common complication of support with CF-LVADs, occurring in 20% to 40% of patients with an incidence of 0.2 to 0.6 events per patient year (2,11-16). GIB is associated with hospital readmissions and invasive procedures resulting in significant resource utilization and decreased quality of life (15-17). Additionally, bleeding events typically lead to interruptions in antithrombotic therapy, which may increase thrombotic complications (15,16,18,19). Moreover, GIB events frequently necessitate blood transfusions, potentially increasing the chance of allosensitization (20). This is particularly problematic in BTT patients in whom the prevalence of sensitization has increased markedly in the CF-LVAD era (20).

Several mechanisms have been implicated in the increased incidence of GIB after implantation of CF-LVADs. The requirement for antithrombotic therapy has increased the incidence of GIB compared to pulsatile-flow LVADs, but bleeding rates far exceed those of other populations requiring anticoagulation (12,21-23). Acquired von-Willebrand factor deficiency has been shown consistently after LVAD implantation, suggesting a role for impaired platelet aggregation (14,24-30). Continuous blood flow and elevated central venous pressure (CVP) have been theorized to increase intraluminal pressure and mucosal ischemia, resulting in a gastrointestinal milieu conducive to angiodysplasia formation (26,31-34). Supporting this theory, low pulsatility index (PI) and persistent aortic valve closure were associated with bleeding in patients supported with the HeartMate II (Thoratec Corp., Pleasanton, California) in a recent study (35). Although our understanding of mechanisms promoting bleeding has improved, predicting which patients may be at increased risk has proven challenging.

Pre-operative risk factors consistently associated with GIB include older age and a history of GIB (14-16,36). Other factors including female sex and ischemic cardiomyopathy have been implicated as risk factors, but these findings have yet to be validated in larger patient cohorts (14,36). The lack of consistent data has precluded development of a pre-operative risk model to identify patients at increased risk of GIB. Right ventricular (RV) dysfunction is associated with poor post-operative outcomes resulting from hepatic congestion, coagulopathy, and diminished cardiac output characterized by low pulsatility and elevated CVP (37,38). Given the theoretical links of these sequelae to bleeding, we hypothesized that assessment of pre-operative RV dysfunction might identify patients at increased risk of post-operative GIB. To address this hypothesis we evaluated the impact of severe pre-operative RV dysfunction on the risk of GIB in patients supported with CF-LVADs.

ABBREVIATIONS AND ACRONYMS

BTT = bridge to transplantation

CF-LVAD = continuous-flow left ventricular assist device

CVP = central venous pressure

DT = destination therapy

GIB = gastrointestinal bleed

PI = pulsatility index

RA = right atrium

RV = right ventricle

TAPSE = tricuspid annular plane systolic excursion

TTE = transthoracic echocardiogram

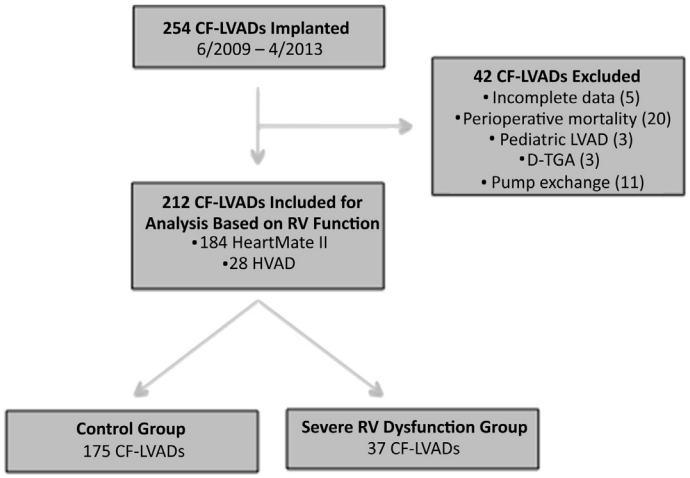
METHODS

STUDY POPULATION. We performed a retrospective cohort study and identified patients who underwent implantation of a HeartMate II or HVAD (HeartWare Corp., Framingham, Massachusetts) LVAD at our institution from June 2009 through April 2013. Two hundred fifty-four patients underwent CF-LVAD implantation during this period. Forty-two patients were excluded from the study primarily due to perioperative mortality or previous pump failure requiring exchange. Detailed exclusion criteria are provided in **Figure 1**. The final cohort for analysis consisted of 212 patients. Validation analysis of CVP and risk of GIB was performed using 173 patients with available invasive hemodynamic data obtained between 48 and 72 h after LVAD implantation. The relationship between duration of post-operative inotrope treatment and GIB was performed using an expanded cohort of 412 LVAD patients (Online Appendix).

We reviewed pre-operative transthoracic echocardiograms (TTE) to assess RV function. All images were obtained according to American Society of Echocardiography guidelines and were interpreted solely by echocardiographic experts prior to, and independent of this study. A comprehensive assessment of RV function was performed considering all available objective and subjective parameters of cardiac function. Based on this assessment, the original interpreting echocardiographer reported the degree of RV dysfunction for each patient. To avoid bias, this original interpretation was then extracted directly from the medical record and patients were divided into cohorts based on the degree of pre-operative RV dysfunction. A severe RV dysfunction cohort consisting of 37 patients with moderate-severe or severe RV dysfunction was compared to a control cohort consisting of 175 patients with normal, mild, mild-moderate, or moderate RV dysfunction.

Patient characteristics including demographics, INTERMACS (Interagency Registry for Mechanically

FIGURE 1 Flow Diagram of Study Design



Shown are detailed exclusion criteria and a breakdown of comparison groups. Perioperative mortality includes all deaths within 30 days of implantation of CF-LVAD. CF-LVAD = continuous-flow left ventricular assist device; D-TGA = D-transposition of great arteries; RV = right ventricle.

Assisted Circulatory Support) data and comorbidities were collected from our institution's electronic medical record. Laboratory data were extracted using the final laboratory measurements before discharge from index hospitalization for implantation of CF-LVAD. Medications were obtained from the discharge medication reconciliation in the medical record. Laboratory data and medications were also collected at the time of hospital readmission for GIB events. Baseline echocardiographic data were collected from the pre-operative TTE report with ancillary measurements obtained from review of original images when missing from the report. Post-operative echocardiographic data were also obtained between 2 and 6 months post-ventricular assist device (VAD) in a similar fashion. Invasive hemodynamic measurements were obtained from pre-operative right heart catheterization records. All data were collected and managed in REDCap (Vanderbilt University, Nashville, Tennessee), an electronic data capture tool hosted by our institution (39). The study was approved by the Institutional Review Board at Washington University School of Medicine.

FOLLOW-UP AND CLINICAL OUTCOMES. Follow-up was assessed for every patient via review of the medical record. The primary outcome was freedom from GIB. GIB was defined as clinically evident or occult GIB prompting hospital admission and endoscopic evaluation. This included patients with gross bleeding from the GI tract, guaiac positivity, or severe anemia requiring blood transfusion in the absence of hemolysis, defined as lactic dehydrogenase >1,000 mg/dl or plasma free hemoglobin >40 mg/dl. Secondary outcomes included incidence of GIB, death, heart transplantation, hemolysis, and epistaxis. Patients were followed from the date of LVAD implantation and were censored after death, heart transplantation, or LVAD removal.

STATISTICAL METHODS. Patient characteristics were compared as appropriate with mean ± SD reported for continuous variables. Between-group comparisons were made using the Student two-sample *t*-test and Fisher exact test for continuous and categorical variables, respectively. Non-normal and ordinal variables were reported as medians (1st quartile, 3rd quartile) and evaluated using the Kruskal-Wallis test. Kaplan-Meier curves were created to evaluate freedom from GIB and the log-rank test was used to compare event-free survival distributions. A multivariable Cox proportional hazards model was created to adjust for age, ischemic cardiomyopathy (ICM) and aspirin strategy, and a hazard ratio for RV dysfunction (vs. control) was reported from this model. We performed 2 validation analyses using post-operative CVP and prolonged duration of inotropes as alternative definitions of RV dysfunction and assessed their ability to predict GIB independently. A secondary analysis was also performed to identify independent predictors of GIB risk. Statistical methods were performed as outlined for the primary analysis above. A 2-sided p value of <0.05 was considered significant. All data analysis was conducted in SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

RESULTS

PATIENT CHARACTERISTICS. The majority of patients in both groups were male (79%) with a median INTERMACS profile of 2 at the time of LVAD implantation (Table 1). Most patients were supported with a HeartMate II in both the severe RV dysfunction and control cohort (92% vs. 86%; p = 0.43). There were no significant differences between cohorts with respect to demographics including age, race, or body mass index. In both groups, 54% of patients were deemed to have ICM, and there were no differences in other relevant comorbidities (Table 1). Laboratory data revealed no differences between groups with respect to post-operative renal and hepatic function (Table 1). Antithrombotic therapy instituted perioperatively resulted in similar

TABLE 1 Patient Characteristics

	Control (n = 175)	Severe RV Dysfunction (n = 37)	p Value
Baseline characteristics			
Age, yrs	57.2 ± 11.7	55.3 ± 12.2	0.38
Male	135 (77.1)	32 (86.5)	0.27
Race			0.39
Black	39 (35.8)	11 (29.7)	
White	136 (64.2)	26 (70.3)	
Other	0 (0)	0 (0)	
BMI, kg/m^2	28.4 ± 5.8	30.0 ± 5.8	0.13
History of GIB	9 (4.2)	1 (2.7)	1.00
Ischemic CMP	81 (46.3)	17 (45.9)	1.00
A fib	73 (41.7)	13 (35.1)	0.58
COPD	27 (15.4)	6 (16.2)	1.00
History of smoking	95 (54.3)	26 (70.3)	0.10
Type of LVAD			0.43
Heartmate II	150 (85.7)	34 (91.9)	
HVAD	25 (14.3)	3 (8.1)	
INTERMACS profile	2 (2, 2)	2 (1, 2)	0.22
DT strategy	57 (32.6)	9 (24.3)	0.12
Medications*			
Aspirin			0.10
0 mg	5 (2.8)	1 (2.7)	
81 mg	85 (48.6)	24 (64.9)	
325 mg	85 (48.6)	12 (32.4)	
PDE5 inhibitor	65 (37.1)	16 (43.2)	0.58
Bosentan	19 (10.9)	11 (29.7)	0.01
Laboratory data*			
Creatinine	1.14 ± 0.63	1.21 ± 0.57	0.49
INR	2.22 ± 0.56	2.24 ± 0.62	0.85
Platelets	317 ± 124	356 ± 118	0.09
Bilirubin	1.0 (0.6, 1.6)	1.2 (0.6, 2.5)	0.32

Values are n (%), mean ± SD, or median (25th percentile, 75th percentile). *On discharge from index hospitalization for implantation of LVAD.

A fib = atrial fibrillation; BMI = body mass index; CMP = cardiomyopathy; COPD = chronic obstructive pulmonary disease; DT = destination therapy; GIB = gastrointestinal bleed; INR = international normalized ratio; LVAD = left ventricular assist device; PDE5 = phosphodiesterase 5; RV = right ventricular.

TABLE 2 Pre-Operative Characteristics

	Control (n = 175)	Severe RV Dysfunction (n = 37)	p Value
Echocardiographic			
TAPSE (cm)	1.50 ± 0.44	1.25 ± 0.36	0.005
RV Tei index	0.59 ± 0.21	0.86 ± 0.22	<0.001
TR severity			0.20
None - mild	113 (64.9)	20 (55.6)	
Mild-moderate - moderate	45 (25.9)	10 (27.8)	
Moderate-severe - severe	16 (9.2)	6 (16.7)	
RAP (mm Hg)	12.04 ± 5.21	14.87 ± 5.38	0.007
RVEDD	3.93 ± 0.74	4.47 ± 0.89	<0.001
LVEDD	6.84 ± 1.16	7.02 ± 0.89	0.38
RV/LV diameter ratio	0.59 ± 0.13	0.64 ± 0.13	0.027
Hemodynamic*			
RAP (mm Hg)	11.9 ± 6.3	14.1 ± 6.4	0.10
PCWP (mm Hg)	24.5 ± 7.2	25.8 ± 5.5	0.36
RAP/PCWP ratio	0.48 ± 0.23	0.57 ± 0.25	0.086
Pre-operative management			
Inotropes	145 (82.9)	31 (83.8)	1.00
Vasopressors	14 (8.0)	3 (8.1)	1.00
IABP	32 (18.3)	11 (29.7)	0.12
Temporary MCS†	7 (4.0)	2 (5.4)	0.66

Values are n (%), mean ± SD, or median (25th percentile, 75th percentile). *On pre-operative right heart catheterization. †Including ECMO, Impella, or RVAD.

ECMO = extracorporeal membrane oxygenation; IABP = intra-aortic balloon pump; LV = left ventricle; LVEDD = left ventricle end diastolic diameter; MCS = mechanical circulatory support; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; RVEDD = right ventricle end diastolic diameter; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation; other abbreviation as in Table 1.

international normalized ratio (INR) levels at discharge between patients with severe RV dysfunction and controls. Aspirin dosage on discharge (81 mg vs. 325 mg) favored low-dose aspirin in the severe RV dysfunction group, but there were no significant differences identified.

PRE-OPERATIVE ECHOCARDIOGRAPHY. Echocardiographic data from TTE performed a median of 7 days before LVAD implantation showed numerous objective differences between the severe RV dysfunction cohort and controls. Notably, tricuspid annular plane systolic excursion (TAPSE) was lower and RV Tei index was higher in the severe RV dysfunction cohort. Analysis of inferior vena cava diameter revealed elevated right atrial (RA) pressure in the severe RV dysfunction cohort when compared with controls. Invasive hemodynamic measurements also showed a trend toward higher RA pressure in the group with severe RV dysfunction. RV end diastolic diameter was increased in the RV dysfunction group when compared to the control group, and there was also a trend toward more severe tricuspid regurgitation in these patients (Table 2).

PERIOPERATIVE MANAGEMENT. Patients in both groups were managed similarly during the perioperative period with a majority receiving intravenous inotropes and nonsignificant differences in usage of intra-aortic balloon pump or other percutaneous mechanical support before LVAD insertion. Although use of phosphodiesterase type 5 (PDE5) inhibitors was similar between groups, use of endothelin antagonists was more common in patients with RV dysfunction (Table 1). Use of bosentan was not associated with an increased risk of GIB (Table 3). Concurrent tricuspid valve repair was performed in a total of 14 patients (6.6%; 7.4% of controls vs. 2.7% of patients with severe RV dysfunction, p = 0.47).

Patients with severe RV dysfunction showed a trend towards requiring more days on inotropes post-operatively (9.0 vs. 7.0; p = 0.08) and more post-operative hospital days (17.0 vs. 16.0; p = 0.20). Only

TABLE 3 Univariate Cox Proportional Hazards Models for GIB Risk

	HR	95% CI	p Value
Age (per 1-yr increase)	1.019	(0.999–1.040)	0.06
Male (vs. female)	0.949	(0.556–1.621)	0.85
Ischemic CMP (vs. no)	1.019	(0.656–1.581)	0.93
History of smoking (vs. no)	1.543	(0.976–2.439)	0.06
History of COPD (vs. no)	1.525	(0.902–2.579)	0.12
History of GIB (vs. no)	1.606	(0.648–3.975)	0.31
BTT strategy (vs. no)	0.558	(0.359–0.867)	0.009
PDE5 inhibitor (vs. no)	0.983	(0.627–1.542)	0.94
Aspirin 325 mg (vs. 81 mg)	1.013	(0.646–1.587)	0.96
Bosentan (vs. no)	0.883	(0.493–1.581)	0.67
Persistent AV closure* (vs. no)	1.199	(0.740–1.943)	0.46
PI* - per 1 unit increase	0.895	(0.657–1.219)	0.48
TV surgery (vs. no)	1.581	(0.722–3.460)	0.25
TAPSE†, per cm increase	0.592	(0.337–1.040)	0.07
RAP† (above vs. below median)	1.712	(1.047–2.798)	0.03
RVEDD†, per cm increase	1.172	(0.889–1.547)	0.26

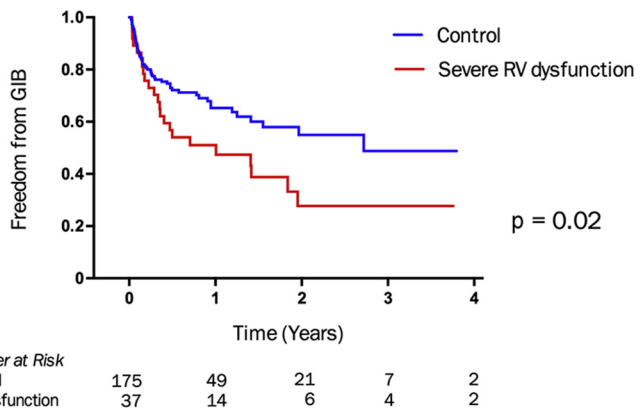
Values are n or median ± SD. *See Online Table 1 in the Online Appendix for details on assessment methods. †As measured on pre–ventricular assist device transthoracic echocardiogram.

AV = aortic valve; BTT = bridge to transplant; CI = confidence interval; HR = hazard ratio; PI = pulsatility index; TV = tricuspid valve; other abbreviations as in Tables 1 and 2.

11 of 212 patients (9 of 175 patients [5.1%] in controls vs. 2 of 37 patients [5.4%] in the severe RV dysfunction cohort) required mechanical RV support. Post-operative measurements of pulsatility revealed no significant differences between groups in aortic valve opening or PI among HeartMate II patients (Online Appendix).

PRIMARY OUTCOME. After a median follow-up of 0.93 (range: 0.46 to 1.83) years, 81 patients had GIB events: 23 of 37 (62%) in the severe RV dysfunction group versus 58 of 175 (33%) in the control group (p = 0.001). Kaplan-Meier analysis revealed statistically significant differences in freedom from GIB over time, p = 0.02 (Figure 2). Differences between groups emerged within months of LVAD implantation with estimated event-free rates of 54% (95% confidence interval [CI]: 0.37 to 0.68) in the severe RV dysfunction cohort versus 72% (95% CI: 0.64 to 0.79) in the control cohort at 6 months (p = 0.04). RV dysfunction remained associated with GIB over time with estimated event-free rates of 31% (95% CI: 0.15 to 0.48) versus 55% (95% CI: 0.44 to 0.65) at 2 years (p = 0.02). After adjustment for age, ICM, and aspirin strategy, severe RV dysfunction remained associated with a higher risk of GIB when compared to controls (Table 4).

FIGURE 2 Pre-Operative RV Dysfunction Is Associated With an Increased Risk of Gastrointestinal Bleeding



Freedom from GI bleed was analyzed using a Kaplan-Meier analysis and log-rank test to compare bleeding rates over time in LVAD patients with severe RV dysfunction **(red line)** compared to control patients without severe RV dysfunction **(blue line)**. The p value is shown. GI = gastrointestinal; LVAD = left ventricular assist device; RV = right ventricular.

Among patients who reached the primary outcome, there were no statistically significant differences between cohorts in INR, platelet count, or aspirin dosing at the time of admission for GIB (Table 5). Multiple GIB events were observed in 35.1% of patients with RV dysfunction compared to 17.1% of controls. There were no differences in location or source of GIB between groups, or in diagnostic procedure utilized to identify bleeding (Online Figures 1 and 2, Online Appendix).

SECONDARY OUTCOMES. Excluding mortality within 30 days of implantation, there were no mortality differences during the total study follow-up period between patients with severe RV dysfunction and controls. There were nonsignificant trends toward increased epistaxis and hemolysis among the severe RV dysfunction cohort (Table 6).

VALIDATION ANALYSES. Although our analysis was initially geared to identify pre-operative factors associated with GIB, we sought to further validate our findings by assessing the association between post-operative parameters of RV dysfunction and the risk of GIB. We chose not to use echocardiographic parameters for this analysis as post-operative TTE is limited by poor image quality, inconsistent timing of study performance, variation of pump speeds, and loss of TAPSE signal (Online Table 1).

Elevated CVP is associated with RV dysfunction and was shown to be a pre-operative predictor of GIB. Patients were stratified by terciles according to post-operative CVP measured at 48 to 72 h after device implantation. After mean follow-up of 12 months, there was a significant association between higher CVP and bleeding (Figure 3A).

Post-operative RV dysfunction is frequently associated with the need for prolonged inotrope support (≥ 14 days) after LVAD implantation. Therefore, in an expanded cohort, we also assessed GIB risk based on

TABLE 4 Cox Proportional Hazards Models

	HR	95% CI	p Value
RV dysfunction	1.799	(1.089–2.973)	0.022
Age (per year)	1.025	(1.004–1.047)	0.022
Ischemic CMP	0.765	(0.556–1.395)	0.27
Aspirin 325 mg	1.156	(0.725–1.842)	0.54

HR for age reported per year of age.
Abbreviations as in Tables 1 and 3.

whether prolonged inotrope support was necessary. Using a cut-off of 14 days, patients requiring prolonged inotrope use were at increased risk of subsequent GIB (Figure 3B).

To further assess the link between RV function and GIB, we compared clinical and RV function parameters in patients who had a GIB versus those who did not. RA pressure was significantly higher in patients with GIB with a strong trend towards significance for reduced TAPSE and increased right ventricular end-diastolic diameter (RVEDD), supporting a link between RV dysfunction and GIB. Persistent aortic valve (AV) closure on echocardiogram and PI did not differ between bleeders and nonbleeders. In addition to RV dysfunction parameters, patients with GIB tended to be older and were implanted with a DT strategy. A history of smoking and chronic obstructive pulmonary disorder (COPD) also trended towards significance in patients with GIB, perhaps related to negative effects of pulmonary disease on RV function (Table 3).

DISCUSSION

GIB remains a significant cause of morbidity in patients with CF-LVADs. Although our understanding of the mechanisms underlying this complication has improved, the identification of risk predictors for GIB events has proven difficult. Only older age and history of bleeding have been consistently implicated as pre-operative risk factors (14–16,36). Acquired von Willebrand factor deficiency has been described in all patients with CF-LVADs and likely reflects shearing of von Willebrand factor multimers (14,24–30). Antithrombotic therapy also has a role in the increased bleeding risk compared to previous generations of LVADs (11,12,21). Given that these factors affect all CF-LVAD patients, we sought to determine additional factors that could be identified pre-operatively that predict an individual's risk of bleeding. GIB in LVAD patients has been partly attributed to angiodysplasias, which account for 30% to 40% of GIB events in these patients (24,26,32,33). Low pulsatility and venous hypertension have been implicated in the development of angiodysplasias (12,26,40,41). RV dysfunction is associated with hepatic congestion, coagulopathy, elevated CVP, and low pulsatility. Therefore, we hypothesized that pre-operative RV dysfunction would identify patients with an increased risk of GIB after LVAD (37,38,42). Consistent with our hypothesis, our analysis revealed a significant association between severe RV dysfunction and GIB in patients supported with CF-LVADs.

In this study we did not pre-specify criteria for the definition of severe RV dysfunction, and instead used the assessment of expert echocardiographers who interpreted the images independent of this study. However, retrospective analysis of the echocardiograms confirmed that the patient cohorts were well separated with regard to objective parameters of RV function including TAPSE, RV Tei, and RVEDD. We observed a modest increase in the duration of post-operative inotropes; however, the need for right ventricular assist devices was not different between the cohorts. This is likely explained by our decision to exclude patients who died in the perioperative period and our institutional practice of not implanting LVADs into patients with clinical RV failure. Accordingly, this data set provided us with a unique opportunity to

TABLE 5 Characteristics on Admission for GIB Event*

	Control (n = 58)	Severe RV Dysfunction (n = 23)	p Value
INR	2.18 ± 0.82	2.30 ± 1.08	0.60
Platelets	220 ± 100	246 ± 102	0.31
Hemoglobin	7.15 ± 1.34	7.34 ± 1.64	0.59
Aspirin			0.33
0 mg	0 (0)	1 (4.3)	
81 mg	26 (44.8)	11 (47.8)	
325 mg	32 (55.2)	11 (47.8)	

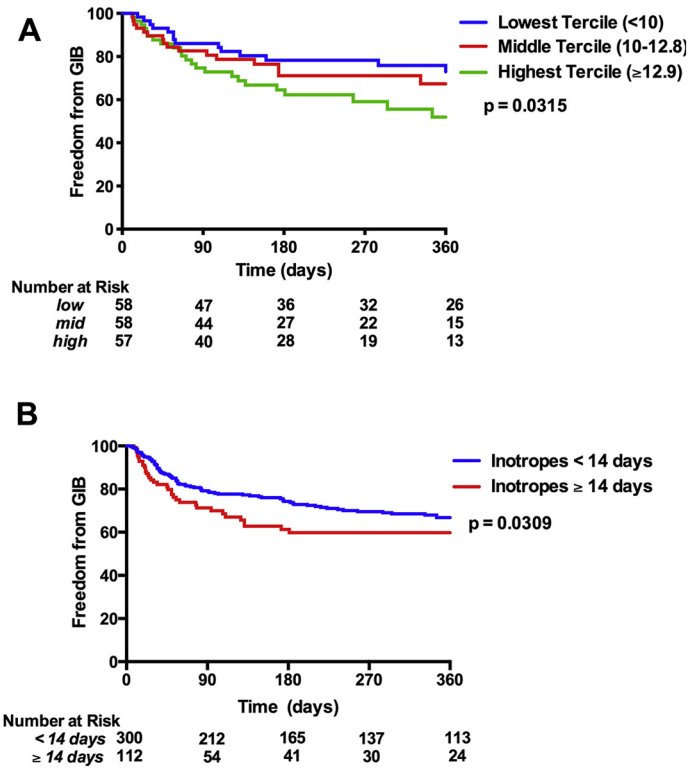
Values are mean ± SD or n (%). *Values taken from admission labs on admission for GIB event.
Abbreviations as in Table 1.

TABLE 6 Secondary Outcomes

	Control (n = 175)	Severe RV Dysfunction (n = 37)	p Value
GIB	58 (33.1)	23 (62.2)	0.001
Death	45 (25.7)	10 (27.0)	0.84
Heart transplant	44 (25.1)	9 (24.3)	1.00
Hemolysis*	24 (13.7)	9 (24.3)	0.13
Epistaxis	12 (6.9)	5 (13.5)	0.19
Multiple GIB	30 (17.1)	13 (35.1)	N/A

Values are n (%). *Hemolysis defined as LDH > 1,00 mg/dl and undetectable haptoglobin on simultaneous collection.
LDH = lactate dehydrogenase; other abbreviations as in Table 1.

FIGURE 3 Hemodynamic and Clinical Markers of Post-Operative RV Dysfunction Are Associated With an Increased Risk of Gastrointestinal Bleeding



(A) Kaplan-Meier analysis comparing bleeding rates over time among patients with low **(blue line)**, mid **(red line)**, or high **(green line)** CVP. **(B)** Kaplan-Meier analysis comparing bleeding rates over time between patients requiring ≥ or <14 days on inotropes post-LVAD, n = 112 **(red line)** vs. 300 **(blue line)** patients, respectively. See the Online Appendix for details. CVP = central venous pressure.

investigate whether RV dysfunction in the absence of severe clinical RV failure could alter the risk of long-term GIB. Indeed, we found that the degree of RV dysfunction on pre-operative echocardiogram was predictive of the risk of GIB after LVAD. To validate this observation, we also evaluated the association between GIB and RV dysfunction using post-operative hemodynamic and clinical definitions. Interestingly, both CVP and prolonged duration of inotrope support after LVAD were also associated with increased risk of GIB, and this persisted out to the first year post-implantation. The fact that the association between pre-operative RV dysfunction on TTE and GIB was confirmed post-operatively using other metrics of RV function further strengthens our observations.

There are several potential mechanisms by which RV dysfunction could increase GIB in CF-LVAD patients. One possibility is increased hepatic congestion with resultant coagulopathy. However, at the time of a GIB event, patients with RV dysfunction had similar INR and platelet counts and used similar antithrombotic strategies to controls, suggesting coagulopathy was not the primary driver of differences in GIB between cohorts. Reduced pulsatility is another mechanism proposed to explain GIB in CF-LVADs, and it is possible that RV dysfunction could decrease pulsatility by underfilling the left ventricle (35). However, neither aortic valve opening nor PI (HeartMate II) were significantly different in our patient cohorts when measured perioperatively and at initial follow-up from the index hospitalization. Univariate analysis of these indices of pulsatility did not reveal an independent association with risk of GIB. Severe RV dysfunction was associated with elevated pre-operative CVP, and our secondary analyses identified elevated CVP as an independent predictor of GIB. Moreover, dividing patients into terciles based on post-operative CVP revealed a graded association between CVP and risk of subsequent GIB. These observations support the hypotheses that the transmission of elevated CVP to the mesenteric circulation could cause venous hypertension in the GI microvasculature. In the setting of continuous blood flow, these changes could theoretically promote ischemia, impair autoregulatory mechanisms via vascular distention, and increase shear stress to promote bleeding from existing angiodysplasias (12,32–34,41). However, it is also possible that elevated CVP may simply be a marker of more severe RV dysfunction.

STUDY LIMITATIONS. We performed this analysis in a retrospective fashion at a single institution and relied on chart review for data collection. Data regarding PI was only available at 2 time points; thus, the lack of association between low pulsatility and GIB should be interpreted accordingly. In addition, we did not have measures of RV function or CVP at the time of a GIB, limiting our knowledge of patient hemodynamics during a bleeding event. Finally, we did not pre-specify criteria for the definition of RV dysfunction by echocardiogram and instead relied on the assessment of the interpreting echocardiographer. However, quantitative echocardiographic and hemodynamic data supported a clear distinction between these patient cohorts. Post-operative hemodynamic and clinical parameters of RV dysfunction were also significantly associated with the risk of GIB.

CONCLUSIONS

GIB remains a significant complication of CF-LVAD therapy. Currently, the ability to predict the risk of bleeding in patients before device implantation is limited. In this study we provide evidence that

pre- and post-operative RV dysfunction is strongly associated with GIB among patients supported with CF-LVADs. Our hemodynamic data suggests that elevated CVP may be part of the mechanism to explain this relationship. Although future studies will be necessary to evaluate the impact of decreasing CVP with diuretics and/or pulmonary vasodilators on the incidence of GIB, we would argue that volume status should be closely managed in LVAD patients with RV dysfunction. To enhance the clinical utility of this data we are currently deriving a GIB risk score based on clinical, echocardiographic, and hemodynamic RV function parameters. If validated, such a tool could be used to trigger pre-emptive adjustments to antithrombotic and CVP lowering strategies and/or better inform the discussion with patients being evaluated for CF-LVADs about the risk of device-associated complications.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: Pre-operative RV dysfunction identifies a subset of patients at increased risk of GIB continuous flow LVAD implantation.

COMPETENCY IN MEDICAL KNOWLEDGE 2: Patients undergoing evaluation for implantation of CF-LVAD should be made aware of risk factors that may influence the risk of long-term device complications.

TRANSLATIONAL OUTLOOK: This study represents an initial step in the development of a risk score that could predict bleeding complications after LVAD implantation.

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APPENDIX For supplemental figures and text, see the online version of this article.