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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