Significantly Higher Rates of Gastrointestinal Bleeding and Thromboembolic Events With Left Ventricular Assist Devices

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BACKGROUND & AIMS: **The risk of gastrointestinal (GI) bleeding (GIB) and thromboembolic events may increase with continuous-flow left ventricular assist devices (CF-LVADs). We aimed to characterize GIB and thromboembolic events that occurred in patients with CF-LVADs and compare them with patients receiving anticoagulation therapy.**

METHODS: **We performed a retrospective analysis of 159 patients who underwent CF-LVAD placement at 2 large academic medical centers (mean age, 55 ± 13 y). We identified and characterized episodes of GIB and thromboembolic events through chart review; data were collected from a time period of 292 ± 281 days. We compared the rates of GIB and thromboembolic events between patients who underwent CF-LVAD placement and a control group of 159 patients (mean age, 64 ± 15 y) who received a cardiac valve replacement and were discharged with anticoagulation therapy.**

RESULTS: **Bleeding events occurred in 29 patients on CF-LVAD support (18%; 45 events total). Sixteen rebleeding events were identified among 10 patients (range, 1–3 rebleeding episodes/patient). There were 34 thrombotic events among 27 patients (17%). The most common source of bleeding was GI angiodysplastic lesions (n = 20; 44%). GIB and thromboembolic events were more common in patients on CF-LVAD support than controls; these included initial GIB (18% vs 4%, $P < .001$), rebleeding (6% vs none, $P = .001$), and thromboembolic events (17% vs 8%, $P = .01$).**

CONCLUSIONS: **Patients with CF-LVADS receiving anticoagulants have a significantly higher risk of GIB and thromboembolic events than patients receiving anticoagulants after cardiac valve replacement surgery. GI angiodysplastic lesions are the most common source of bleeding.**

Keywords: Heart Failure; Treatment; Complication; Morbidity; Hemorrhage.

Left ventricular assist device (LVAD) implantation results in improved survival and quality of life in patients with advanced heart failure.[1] Second-generation continuous-flow LVADs (CF-LVADs) frequently are used as a bridge to cardiac transplantation and as destination therapy (LVAD placement without planned transplantation). CF-LVADs show improved durability and longer patient survival compared with first-generation pulsatile-flow LVADs. In addition, CF-LVADs are much smaller in size compared with pulsatile-flow devices.[2,3] Despite the improved survival associated with CF-LVADs, significant morbidity exists, partly related to bleeding diathesis. Gastrointestinal (GI) bleeding (GIB) has been reported to occur in approximately 18% to 23% of these patients,[2,4,5] with rates as high as 40% reported in some studies.[6] Formation of gastrointestinal angiodysplastic lesions (GIADs) have been reported to occur at increased rates in patients after CF-LVAD implantation,[7] possibly owing to narrowed pulse pressures that mimic aortic stenosis.[8] Patients who receive CF-LVADs also show findings consistent with an acquired von Willebrand disease, which likely results in an increased risk of bleeding.[9–11]

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Abbreviations used in this paper: **CF-LVAD, continuous-flow left ventricular assist device; CVA, cerebral vascular accident; DVT, deep vein thrombosis; GI, gastrointestinal; GIAD, gastrointestinal angiodysplastic lesion; GIB, gastrointestinal bleeding; INR, international normalized ratio; LVAD, left ventricular assist device.**

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CF-LVAD use requires anticoagulation and antiplatelet therapy because of the hypercoagulable state associated with a blood-device interface. Earlier-generation LVADs reported thromboembolic rates up to 30%.[7] Newer, second-generation LVADs appear to have a lower incidence of thromboembolic events, although data regarding these events have been limited. The newer LVADs are smaller in size; therefore, the associated decreased surface area in contact with the bloodstream is believed to be responsible for the decreased rate of thrombosis associated with these specific devices.[12] However, thromboembolic events, although decreased, continue to occur in approximately 1% to 6% of LVAD patients.[2,7,13]

There have been several studies describing the rate of GIB and thromboembolic events in LVAD patients. Our aim was to characterize GI bleeds and thromboembolic events that occurred in patients with CF-LVADs and compare them with an anticoagulated control population. Our hypothesis was that LVAD patients would show higher rates of both GI hemorrhage and thromboembolic events compared with a control group that was receiving anticoagulation after cardiac valve replacement.

Methods

After obtaining institutional review board approval, we retrospectively reviewed charts of all patients who underwent CF-LVAD implantation from January 1, 2009, through July 31, 2011, at the University of Virginia Medical Center, and from June 30, 2010, through June 20, 2013, at the Stanford University Medical Center. Patients who died within the first 7 days after LVAD placement were excluded from our analysis. Demographic data, presence and etiology of GIB, and presence and etiology of thromboembolic events were recorded through a review of electronic medical records.

A retrospective chart review also was used to construct a control group of patients requiring anticoagulation after cardiac valve replacement surgery. We identified 709 consecutive patients who received cardiac valve replacements between January 1, 2009, and October 31, 2011, at the University of Virginia. Of the 709 patients who underwent valve replacement surgery, 159 total patients required anticoagulation at discharge and represented the control group. Demographics, GIB, and thromboembolic events were collected in the control group. Patients who received valve replacements and CF-LVADs concurrently were included in the CF-LVAD group ($n = 5$).

GIB events were defined as a decrease in hemoglobin of at least 2 g/dL with passage of melena, bright red blood per rectum, hematemesis, coffee-ground emesis, or heme-positive stools. The location and etiology of GI bleeds were confirmed by direct endoscopic visualization, angiography, or nuclear medicine–tagged red blood cell scans in nearly all cases. Patients underwent upper endoscopic examination in the presence of melena and/or hematemesis and colonoscopy as the initial test when presenting with hematochezia when medically stable. If the initial endoscopic examination was normal, testing via the opposite direction typically was performed. Video capsule endoscopy, nuclear medicine bleeding scans, and/or angiography could be performed at the discretion of the attending gastroenterologist if no source of bleeding was detected on both upper and lower endoscopic examinations. Deep enteroscopy could be performed if capsule endoscopy showed findings warranting endoscopic therapy or further investigation. Some patients were classified as unknown without having undergone all testing modalities depending on their clinical status and the discretion of the gastroenterologist.

Thromboembolic events (cerebral vascular accident [CVA], deep vein thrombosis [DVT], superficial vein thrombosis, pulmonary embolus, splenic infarct, and myocardial infarction) were confirmed with a radiologic study (ultrasound, computed tomography, magnetic resonance imaging, or cardiac catheterization). LVAD thrombosis was diagnosed based on device explant or autopsy, computed tomography angiogram, and/or strong clinical suspicion owing to device power spikes, evidence of new hemolysis, and/or positive ramp echocardiography in the absence of an alternative explanation.

The primary end points of the study were the frequency of GIB and thromboembolic events in both groups. Secondary end points included the location and etiology of GI bleeds and thromboembolic events, international normalized ratio (INR) at time of GI bleed, and number of rebleeding events (recurrent episodes of GIB).

Statistical Analysis

The patient characteristics between the 2 groups were compared using the Student *t* test for normally distributed continuous variables, the chi-square test for categoric variables, and the Fisher exact test for categoric data with infrequent occurrences using SAS (version 9.3; SAS Institute, Cary, NC). All *P* values were 2-sided, and a *P* value of .05 or less was considered statistically significant.

Based on the prior literature, we assumed that the rate of GIB would be approximately 20% for the LVAD cohort compared with 14% for patients status-post valve replacement surgery.[14–16] By using an α value of 5% and a power of 80%, the estimated sample size was 120 patients in each group.

Results

Continuous-Flow Left Ventricular Assist Device Cohort

A total of 159 patients (age [mean $\pm$ SD], 55 $\pm$ 13 y; range, 18–81 y) met our inclusion criteria. One patient