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Adverse Events in Continuous-Flow LVAD Recipients: Gastrointestinal Bleeding is Still Notable?

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Abstract

Background

The etiology and risk factors associated with gastrointestinal bleeding (GIB) in patients with continuous-flow left ventricular assist devices (CF-LVADs) are currently unknown. Therefore, we sought to assess the risk factors for GIB in these patients.

Design and Methods

This was a retrospective, non-randomized, non-controlled study at a single center. Between 2012 and 2014, 65 men and 6 women (mean age = 55 ± 12 years) underwent CF-LVAD implantation at our institution. Overall, 23.9% of patients (17/71) had at least one GIB episode. Endoscopy confirmed GIB in 13/17. Arteriovenous malformation was the major GIB source in 8/13 (61%). There was no significant difference in incidence of GIB with regard to INTERMACS profile, blood type, or device type—HeartWare vs. HeartMateII. All our patients with GIB were men, most had hyperlipidemia, and most likely had ischemic cardiomyopathy

(65%) and peripheral vascular disease (24%). The only significant risk factor for GIB was chronic kidney disease (odds ratio= 3.95; 95% confidence interval of 1.21 to 12.84; *p*=0.02). At the time of the first GIB, mean hemoglobin was 7.38 ± 1.06 g/dl, international normalized ratio was 2.08 ± 0.69 IU, and mean arterial pressure was 75 ± 12 mmHg. Ten patients (59%) required hospital admission for treatment.

Conclusion

In our patients GIB was often a single event and often occurred within first month after implantation. Prevention strategies should be focused on this vulnerable period, especially in patients with chronic kidney disease

Keywords: gastrointestinal bleeding, left ventricular assist device (LVAD), heart failure, thromboembolic event

Introduction

The use of a left ventricular assist device (LVAD) either as a bridge to transplantation or a destination therapy has significantly improved survival for end-stage heart failure patients.[1,2] The new generation of continuous flow devices have favorable characteristics; they are small, durable, and are associated with fewer adverse events than pulsatile LVADs. Nevertheless, important comorbidities associated with these devices do exist, and they are partly related to bleeding diathesis. Bleeding complications following LVAD implant are common and contribute significantly to morbidity and mortality. Overall bleeding rates are in the range of 45% to 55% with gastrointestinal bleeding (GIB) occurring in approximately 25% of patients with LVADs.[1,3-6] This results in hospital readmissions and treatment, which increases the total cost of care considerably.

It has been suggested that reduced pulse pressure induced by CF-LVADs results in hypoperfusion of the gastrointestinal mucosa and neovascularization in friable vessels that are prone to bleeding.[7] These gastrointestinal angiodysplastic conditions are found at increased rates in patients after CF-LVAD implantation.[4,8] The high incidence of bleeding has also been attributed to the development of acquired von Willebrand syndrome (AVWS), which is a deficiency of the high molecular weight von Willebrand multimers (HMWM).[9,10] The shear forces on blood components created by continuous flow LVADs damage and inactivate HMWM. The complex interaction between a patient's innate hemostatic characteristics, anatomical predisposition for bleeding, AVWS, and anticoagulation therapy all contribute to the development of the bleeding complications.[11] Management of GIB requires alteration of anticoagulation and antiplatelet therapy, consequently complicating the already altered thrombotic profile and increasing the risk of thromboembolic (TE) events, including pump thrombosis.[5]

The aim of this study was to identify the characteristics of patients who had undergone implantation of a CF-LVAD and had experienced nonsurgical GIB events. We sought to evaluate risk factors that make these patients prone to GIB

and determine their additional TE hazard in order to improve management of this complication.

Methods

Study Population

This single-center retrospective study included 71 patients (65 men and 6 women) underwent implantation of a CF-LVAD; HeartMate II (Thoratec Corporation, Pleasanton, CA) (HMII) 50 patients, and HVAD (HeartWare Inc., Framingham, MA) in 21 patients. Pre-operative clinical characteristics were recorded for all patients and included INTERMACS profile, presence of coronary artery disease, peripheral vascular disease, diabetes, presence of a known GI disease, prior stroke, chronic kidney disease, atrial fibrillation, hypertension, and hyperlipidemia. The Institutional Review Board approved the study and all patients gave informed consent for participation.

After LVAD implantation, patients were started on intravenous heparin and transitioned to oral anticoagulation therapy with warfarin between postoperative days 2 and 5. Thereafter, all patients received 81mg aspirin and warfarin to achieve the target INR of 2–3 IU. Additional antiplatelet therapy with 75mg dipyridamole 3 times per day was given in 2 of 71 patients who had developed device thrombosis. Platelet function was monitored by light transmittance aggregometry in all patients pre-operatively and during bleeding episodes. The pump speed setting of both devices was determined by ramp speed echocardiogram studies. During the first 24 hours after implantation in patients with the HMII, pump speed was increased under echocardiographic guidance up to 8800 revolutions per minute (RPM) to allow aortic valve opening with a ratio of 1:3. In HVAD-supported patients, pump speed was increased up to 2800 RPM. Later, pump speed was optimized on the basis of patient symptoms, suction events, and echocardiographic evaluation.

Outcome Assessment

Major bleeding was defined as an episode of suspected internal bleeding resulting in transfusion of packed red blood cells (RBCs), hospitalization, surgical intervention, or death.[7] In specific cases, GIB was defined by clinical evidence of bleeding (guaiac-positive stool, melena, hematemesis, hematochezia, or the presence of blood in the GI tract on endoscopic evaluation) with a decrease in hemoglobin (Hb)≥ 2 g/dl compared to the patient's Hb value at the time of the last follow-up. Multiple bleeding events during the same hospitalization were counted as the same event. Patients underwent upper endoscopic examination (esophagogastroduodenoscopy or small-bowel enteroscopy) in the presence of melena and/or hematemesis and underwent colonoscopy when presenting with hematochezia and medically stable. Gastrointestinal bleeding was categorized as upper GIB, proximal to the ligament of Treitz, or lower GIB, distal to the ligament of Treitz.

Anticoagulation therapy was discontinued until active GIB stopped. The decision to restart anticoagulation therapy was based on clinical assessment after the remission of active GIB. Treatment options for bleeding vessels were endoclips with epinephrine injections or cauterization (argon plasma coagulation or gold probe cauterization). Additionally, medical gastro-protective therapy with proton pump inhibitors was utilized.

We also analyzed patients on LVAD support for thromboembolic (TE) events (stroke**,** transient ischemic attack, and confirmed or suspected pump thrombus), hemolysis, right heart failure, respiratory failure, renal and hepatic dysfunction, and survival. The primary goal of this study was to analyze the frequency of GIB as well as the location and etiology of GIB in both LVAD groups. The frequency of TE events was analyzed as well. Median follow-up and LVAD support was 6 months (3 to 23months).

Statistical Analysis

Data analysis used SPSS 22.0 statistical software (SPSS, Inc., Chicago, IL), and values are expressed as mean ± standard deviation for normally distributed data or as medians with ranges for non-normally distributed continuous data. Categorical data are presented as percentages. Student's t-test and the independent samples Mann–Whitney test for continuous variables or the chi-square test for categorical data were used to compare data between the two groups. Fisher's exact test was used when appropriate. Logistic regression analysis was used to identify risk factors for GIB. A p value <0.05 was considered statistically significant.

Results

Twenty-five GIB episodes were recorded in the 17/71 (23.9%) patients. Patients with GIB were all men, with a mean age of 59 ± 8 years. Median time to the first GIB episode was 21 days (range, 11 to 140 days), with 11/17 episodes occurring within first month after the pump implantation. Fourteen patients had a single episode, and 3 patients had multiple bleeding episodes (3, 4, and 4 bleeding episodes, respectively). The second bleeding episode occurred 20, 24 and 110 days after the first bleeding episode, respectively. All patients with multiple GIBs had HMII pump.

Preoperative data for patients with GIB and those without are shown in Table 1. In patients with GIB, significantly more patients had chronic kidney disease, and more patients had hyperlipidemia, but the latter difference did not reach significance. Two patients had known past medical history of GI peptic ulcers. On logistic regression analysis, the only risk factor significant for GIB was the presence of chronic kidney disease (odds ratio=3.95; 95% confidence interval of 1.21 to 12.84; p=0.02).

Table 1. Baseline Patient Characteristics

	GIB (N=17)	Non-GIB (N=54)	*p* Value
Age (year)	59 ± 8	54 ± 13	0.145
Men/women	17/0	48/6	0.151
Body mass index (kg/m^2)	29.1 ± 6.3	29.9 ± 7.0	0.699
Heart disease			0.289
Ischemic cardiomyopathy	11 (65)	27 (50)	
Idiopathic cardiomyopathy	6 (35)	27 (50)	
Diabetes mellitus	12 (71)	28 (52)	0.174
Hypertension	14 (82)	45 (83)	0.925
Hyperlipidemia	12 (71)	23 (43)	0.055
Myocardial infarction	9 (53)	25 (46)	0.632
Peripheral vascular disease	4 (24)	5 (9)	0.123
Chronic kidney disease	11 (65)	16 (30)	0.019
Atrial fibrillation/flutter	8 (47)	17 (32)	0.241
Chronic obstructive pulmonary dis.	2 (12)	6 (11)	0.941
Stroke	4 (24)	4 (7)	0.067
GI ulcer	1 (6)	1 (2)	0.381
LV ejection fraction (%)	19 ± 5	20 ± 7	0.343
LV end-diastolic dimension (cm)	6.8 ± 0.8	6.5 ± 1.2	0.476
Mean arterial pressure (mmHg)	88 ± 14	82 ± 12	0.163
Sodium (mEq/L)	137 ± 4.0	137 ± 4.9	0.807
Blood urea nitrogen (mg/dl)	29.8 ± 17	31.7 ± 19	0.713
Creatinine (mg/dl)	1.83 ± 1.4	1.62 ± 0.8	0.430
AST (IU/L)	30 (17–203)	34 (4–789)	0.558
ALT (IU/L)	36 (20–289)	36 (8–1574)	0.848
Total bilirubin (mg/dl)	0.8 (0.4–10.7)	1.0 (0.4–120)	0.327
Albumin (g/dl)	2.9 ± 0.63	3.02 ± 0.55	0.631
INR (IU)	1.2 ± 0.2	1.4 ± 0.6	0.383
Device			0.554
HVAD	6 (35)	15 (28)	
HMII	11 (65)	39 (72)	
BTT/DT	14/3	28/26	0.026
Intensive care unit stay (days)	9 ± 5	16 ± 18	0.321
Pre-implantation support			
ECMO	0 (0)	5 (9)	0.189
IABP	3 (18)	10 (19)	0.910
TandemHeart	2 (12)	7 (13)	0.877
Blood type			0.805
O	9 (53)	27 (50)	
A	5 (29)	15 (28)	
B	3 (18)	9 (17)	
AB	0 (0)	3 (5)	
INTERMACS score			0.231
1	5 (29)	20 (37)	
2	7 (41)	13 (24)	
3	3 (18)	16 (30)	
4-7	2 (12)	5 (9)	

Results are presented as mean ± standard deviation, median (range), or number of patients (%).

Abbreviations: GIB, gastrointestinal bleeding; ALT, alanine amino transferase; AST, aspartate amino transferase; BTT, bridge-to-transplant; DT, destination therapy; ECMO, extracorporeal membrane oxygenation; GI, gastrointestinal; HMII, HeartMate II; HVAD, HeartWare; IABP, intra-aortic balloon pump; INR, international normalized ratio; LV, left ventricle.

All patients with GIB presented with anemia — also, 8 with melena, 1 with hematemesis, 6 without obvious bleeding source, and 2 with only positive guaiac stool test. Esophagogastroduodenoscopy (EGD), small-bowel enteroscopy, and colonoscopy confirmed bleeding sources in 13 patients. Arteriovenous malformations (AVMs) were identified as the major source of bleeding in 8/13 patients (61%). The location of the first incidence of GIB is summarized in Table 2.

Table 2. Location of the First Gastrointestinal Bleeding Event after Left Ventricular Assist Device Implantation

Location	N
Upper GI	9
Mallory–Weiss tear	1
Gastric AVM	2
Gastric ulcer	1
Gastric polyp	1
Duodenal AVM	2
Jejunal AVM	2
Lower GI	6
Cecal AVM	1
Cecal ulcer	1
Distal transverse colon ulcer	1
Sigmoid colon diverticulosis	1
Sigmoid colon AVM	1
Rectal AVM	1

Abbreviations : GI – gastrointestinal, AVM-arteriovenous malformations

In 2 patients endoscopy confirmed bleeding from 2 sources during the same GIB episode. One patient had both gastric and jejunal AVM. The other patient had rectal AVM and sigmoid colon diverticulosis. In 1 patient, the small bowel AVM was identified only by on-table push enteroscopy because EGD, colonoscopy, nuclear medicine study, and angiograms failed to diagnose the bleeding source.

GI endoscopy was not performed in 2 patients—1 with melena and 1 without obvious bleeding source—due to hemodynamic instability. In another 2 patients, conclusions were made by guaiac-positive stool tests only. These 4 patients experienced single bleeding episodes. For the 17 patients with GIB, characteristics at the time of the first bleeding episode are shown in the Table 3. All patients had body mass index (BMI)>18.5kg/m^2 at the time of the GIB. Patients with multiple GIBs displayed trends toward higher INR values, lower PTT values, and lower creatinine levels (Table 4). Only 1 patient with multiple GIB episodes was diagnosed with coagulopathy (factor deficiency in the common or in both intrinsic and extrinsic pathways), and one patient had GIB whenever his INR value exceeded 2IU**.**

Table 3. Patient Characteristics at the Time of the First Gastrointestinal Bleeding Event

	GIB (N=17)
Hemoglobin (g/dl)	7.38 ± 1.06
INR (IU)	2.08 ± 0.69
Prothrombin time (s)	23.21 ± 5.81
Partial thromboplastin time (s)	48.15 ± 12.5
Platelet count	232 ± 98
Blood urea nitrogen (mg/dl)	33 ± 15
Creatinine (mg/dl)	2.02 ± 1.33
Albumin (g/dl)	2.35 ± 0.49
Mean arterial pressure (mmHg)	75 ± 12
Discharge INR (IU)	1.65 ± 0.52

Results are presented as median (range), mean ± standard deviation, or number (%).
Abbreviations: N, number of patients with gastrointestinal bleeding; INR, international normalized ratio; RBC, red blood cells.

Table 4. Characteristics of Patients with Single and Multiple GIB

Parameter	Single GIB (N=14)	Multiple GIB episodes (N=3)*	*p* Value
INR (IU)	1.86 ± 0.5	2.49 ± 1.33	NS
Partial thromboplastin time (s)	49 ± 11	36 ± 14	NS
Creatinine (mg/dl)	2.4 ± 1.6	1.4 ± 0.3	NS
Albumin (g/dl)	2.34 ± 0.5	2.23 ± 0.7	NS
Right heart dysfunction (n)	11	1	NS

Abbreviations: NS, not significant; GIB, gastrointestinal bleeding; INR, international normalized ratio.* Average of all episodes.

Of the 17 patients with GIB, 7 were hemodynamically stable (MAP> 70 mmHg, Hb≥ 7.0 g/dl, and INR <3.5 IU) when presenting at hospital. The other 10 required additional medical management for hemodynamic instability while hospitalized. LVAD operating parameters at the time of GIB episode and at 30-day follow-up are shown in Table 5.

Table 5. LVAD Operating Parameters at 30-Days after LVAD Implant and at the First GIB Episode

	Patients without GIB at 30 days on LVAD	Patients with GIB at 30 days on LVAD	Patients with GIB at first GIB episode	*p* Value
HMII	N=39	N=11	N=11	
Pump speed (RPM)	8400 (7990–9000)	8800 (8200–9000)	8400 (8000–9000)	0.069
Pump flow (LPM)	5 (2.9–8.5)	4.8 (4.3–6.3)	5.5 (4.4–7.7)	0.876
Pump power (W)	4.8 (3.9–6.8)	5 (4.3–6.9)	5.4 (4.1–7.5)	0.113
Pulsatility index	6.2 (4–8)	5.6 (3.8–8.7)	6.1 (3.8–8.6)	0.626
Pulsatility (y)	14	3	11 (58)	0.828
MAP (mmHg)	78 ± 11	78 ± 10	78 ± 12	0.741
HVAD	N=15	N=6	N=6	
Pump speed (RPM)	2500 (2400–2800)	2580 (2500–2600)	2560 (2500–2600)	0.467
Pump flow (LPM)	5 (3.8–7.3)	5.5 (5.0–6.2)	4.9 (4.6–5.7)	0.387
Pump power (W)	3.4 (2.7–4.8)	3.7 (3.0–4.0)	3.4 (3.2–3.4)	0.765
Pulsatility index	n/a	n/a	n/a	n/a
Pulsatility (y)	9	4	0	0.023
MAP (mmHg)	75 ± 8	77 ± 10	70 ± 12	0.701

Results are presented as median (range), mean ± standard deviation, or number.
N, number of patients.
n/a, not applicable.

Abbreviations: GIB, gastrointestinal bleeding; HMII, HeartMate II; HVAD, HeartWare; LPM, liters per minute; RPM, revolutions per minute; MAP, mean arterial pressure.

Patients with multiple GIB episodes received, on average, 3.5 units of RBCs plus 2 units of fresh frozen plasma (FFP) at the second bleeding episode and 2.5 and 2 units of RBCs at the third and fourth bleeding episode, respectively. There were no platelet transfusions or cryoprecipitate transfusions. After discharge from the first GIB episode, the majority of patients were restarted on both aspirin and warfarin therapy (92%), with only 1 patient restarted on triple warfarin-aspirin-dipyridamole therapy.

There were 3 TE events in our group of patients with GIB: 1 transient ischemic attack 345 days after device implantation, 1 stroke 53 days after device implantation, and 1 confirmed device thrombosis 86 days after LVAD placement. Two patients had thromboembolic events at 26 days and 24 days after the GIB event. The first patient had multiple GIB events and was receiving only aspirin at the time of the event. He subsequently underwent heart transplantation for device thrombosis (not pump replacement). In total 3 patients with GIB underwent heart transplantation. One patient with GIB died of multiple organ failure within 30 days after LVAD implantation.

Discussion

In summary, pump thrombosis has been and continues to remain a major adverse event during destination therapy. Pump thrombosis may have been initially underestimated. Aggressive monitoring of anticoagulation and hemolysis is the sine qua non of pump thrombosis prevention. We observed GIB complications in nearly 25% our patients supported with CF-LVADs, with no difference between the types of LVADs. AVMs were the most common etiology. Overall, patients with and without GIB had similar pre-implantation characteristics, perioperative adverse events, and survival rates. The majority of our patients with GIB received LVAD support as a bridge to transplant, and they were not statistically older than patients without GIB, which has been recognized as a risk factor in previous studies.[12] The only patient characteristic that was significantly associated with GIB was the presence of chronic renal insufficiency. This has been linked with nonsurgical bleeding in different clinical settings.[7,12,13] . All our patients with GIB were male, most had hyperlipidemia, and most likely had ischemic cardiomyopathy (65%) and peripheral vascular disease (24%).

Previously, it has been shown that patients with O blood type have lower levels of measured von Willebrand factor and factor VIII.[15] However, in our study group, the presence of blood type O was not associated with increased risk of bleeding. In 88% of our patients, bleeding events occurred in the absence of supratherapeutic anticoagulation, with no patient having an INR> 4.[7,14] No abnormality was observed in baseline platelet function of patients with GIB. The AVWS, LVAD pump speed, lack of pulsatility, and platelet aggregation have been implicated in the increased incidence of bleeding in CF-LVADs. In our study group, HMWMs

were not routinely measured, but recently published papers show that AVWS is found in all patients with CF-LVADs.[16-18]

Treatment for GIB involves decreasing INR goals and withholding antiplatelet and anticoagulation medications. This places the patient at increased risk of TE events while on VAD support.[19,20] The patient with documented pump thrombus in our study previously had multiple GIB events and was receiving only 81mg aspirin at the time of thrombosis. Patients with stroke and TIA had both anticoagulation and antiplatelet therapy at the time of their TE events. Our institutional policy for anticoagulation and antiplatelet therapy after the first GIB event is warfarin with 81mg aspirin and a target INR of 1.5–2. If there is recurrence of GIB after the first event, patients will still receive warfarin to achieve a target INR of 1.5–2 but without any antiplatelet therapy. After a third event, patients are discharged with all anticoagulation and antiplatelet therapy withheld.

For patients with multiple GIB events, testing for coagulopathy should be utilized as an additional diagnostic measure to determine desirable INR in that subpopulation of LVAD recipients. It was shown that LVAD patients have an increase in activated endothelial cells, which leads to expression of inflammatory markers that can promote coagulopathies in addition to the hypercoagulable state and predisposition of platelet activation due to direct contact between blood and the foreign material of the LVAD.[3,21] Patients with multiple GIB events when INR>2IU helped us determine our institutional policy for anticoagulation and antiplatelet therapy after the bleeding event. Prior to bleeding events, our patients are generally prescribed warfarin with INR goals of 2–3, but therapy is often discontinued after patients experience GIB and is then restarted after GIB resolves. None of the confirmed GIB events were fatal in our study group.

It has been hypothesized that a lower pump speed in an LVAD may result in higher pulse pressures and fewer GIB events.[22] Conversely, higher pump speed may result in decreased capillary pressure and ischemia in the GI mucosa in addition to AVWS.[21] Also, a lower LVAD pump speed may cause less dispersal of heat and increased propensity for clot formation.[23] In theory, the HVAD contact-free design and lower pump speed should provide cardiac support with lower levels of sheer stress, preserving HMWM.[16,17] Although the HVAD pump speed is low, it still reaches a sufficient threshold to induce von Willebrand factor unfolding and loss of HMWM, with higher speed corresponding to greater loss of HMWM.[16,17] The association between severe right ventricular (RV) dysfunction and increased bleeding risk could also be related to a more advanced stage of heart failure.[7] Patients with severe RV dysfunction can present clinically with low LVAD flows and low pulsatility index, which could additionally explain the association between RV dysfunction and bleeding risk.[7] Similarly, severe RV dysfunction and portal hypertension are associated with malnutrition, and abnormal liver function increases risk of bleeding.[24,25] It should be noted that the sample size in this study may have limited the study's ability to detect statistically significant differences in some of the variables compared. Similarly, this study consisted of patients receiving LVAD support mainly as bridge-to-transplant therapy, which may have selected for certain patient characteristics. Also, von Willebrand factor multimers were not routinely measured. Future prospective multicenter trials are still needed to further assess the mechanisms of GIB and TE events.

As the number of patients receiving LVAD support grows worldwide, it is expected that adverse bleeding events will increase, with a significant increase of cost for patient hospitalization and management.[1,7] For these patients, standard upper endoscopy and colonoscopy, offered as diagnostic and therapeutic medical procedures, as well as video capsule or surgical push enteroscopy can be performed in an outpatient setting with gastrointestinal protective therapy (proton pump inhibitors), interruption of warfarin therapy, and iron supplements. Afterward, a new regimen for anticoagulation therapy can be designed for the patient. Patients requiring blood transfusion, FFP, cryoprecipitate, or Vitamin K antagonist therapy would be managed in an outpatient setting as well. Management of these patients with such a plan requires a team-based approach and good coordination among cardiologists, gastroenterologists, and hematologists in an outpatient setting.

This was a retrospective, non-randomized, non-controlled study at a single center. The limited sample size and patient characteristics make comparison to other reports difficult. Although the percentage of patients with GIB was comparable to other studies, the median time to the first GIB event in our study was only 21 days—considerably earlier than other reports.[20,26] However, other studies have shown that the time to first GIB is as soon as 8 days[27] and as long as 383 days[28], and the range in our study was 11 to 140 days. Although we did not investigate this phenomenon, we suspect that some factors that may influence the time to first GIB are severity of illness, renal disease, age, gender, anticoagulation and antiplatelet therapy, prior GI pathology and degree of AVWS. More studies are needed to better understand both the time of first GIB and the time to recurrence of GIB.

In conclusion, GIB occurs mainly as a single event that is widely variable in timing, but may present within the first month after surgery. Therefore, prevention strategies should be focused on this vulnerable post-implantation period, especially in patients with chronic kidney disease.

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