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EDITORIAL

Bleeding with the artificial heart: Gastrointestinal hemorrhage in CF-LVAD patients

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Abstract

Continuous-flow left ventricular assist devices (CF-LVADs) have significantly improved outcomes for patients with end-stage heart failure when used as a bridge to cardiac transplantation or, more recently, as destination therapy. However, its implantations carries a risk of complications including infection, device malfunction, arrhythmias, right ventricular failure, thromboembolic disease, postoperative and nonsurgical bleeding. A significant number of left ventricular assist devices (LVAD) recipients may experience recurrent gastrointestinal hemorrhage, mainly due to combination of antiplatelet and vitamin K antagonist therapy, activation of fibrinolytic pathway, acquired von Willebrand factor deficiency, and tendency to develop small intestinal angiodysplasias due to increased rotary speed of the pump. Gastrointestinal bleeding in LVAD patients remains a source of increased morbidity including the need for blood transfusions, extended hospital stays, multiple readmissions, and overall mortality. Management of gastrointestinal bleeding in LVAD patients involves multidisciplinary approach in stabilizing the patients, addressing risk factors and performing structured endoluminal evaluation with focus on upper gastrointestinal tract including jejunum to find and eradicate culprit lesion. Medical and procedural intervention is largely successful and universal bleeding cessation occurs in transplanted patients.

Key words: Gastrointestinal bleeding; Left ventricular assist devices; Heart failure; Angioectasia; Endoscopy

Core tip: Classic descriptors and latest developments in care of left ventricular assist devices (LVAD) patients presenting with gastrointestinal (GI) hemorrhage. Pathophysiology, etiology, clinical presentation, risk factors, location within the GI tract, differential diagnosis, management, complications, and prognosis of LVAD patients with GI hemorrhage. Comprehensive review of aspects of clinical care and future research in this patient population.

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INTRODUCTION

Continuous-flow left ventricular assist devices (CF-LVADs) are the current standard-of care for end stage heart failure, having virtually replaced older pulsatile flow devices due to the smaller size, durability and improved survival outcomes[1,2]. First used experimentally in the late 1960s, LVADs have undergone multiple changes and advances, both structural - becoming smaller and more portable, and functional - changing from pulsatile to continuous flow models. Increased survival and improved quality-of-life in patients with LVADs has lead to significant increase in popularity and utilization among patients and providers over the last decade. The annual rate of device placement in the United States alone has been steadily increasing from 206 LVADs in 2006 to 1451 in 2010, with an overall unchanged rate of heart transplant[3]. The use of the device has also been expanded significantly, as both a bridge-to transplant and a long-term use as destination therapy, especially in patients for whom heart transplant is not an option[1,2]. This increasingly prolonged utilization has led to compounded recognition of additional complications, including gastrointestinal bleeding (GIB)[4].

GIB significantly impacts patient's morbidity and mortality. The annual incidence of gastrointestinal (GI) hemorrhages ranges from 50 to 150 per 100000 of the population of the United States[5]. Upper gastrointestinal tract bleeding (UGIB), from lesions proximal to the ligament of Treitz is responsible for about 20000 deaths annually in the United States[6]. Peptic ulcer disease remains the commonest cause, accounting for nearly 60% of all UGIB[7]. Lower GIB is responsible for 50% as many hospitalizations as upper GIB and carries a mortality rate of 2.4%-3.9%[8]. CF-LVAD recipients are more likely to have a GIB than the general population, and of greater severity, requiring an average of 2-4 units of packed red blood cells per admission[9]. In fact, GIB is the most common adverse event and a frequent cause for early post-transplant readmission in LVAD patients[10]. Historically, 15%-61% of the patients may develop GI hemorrhage after LVAD transplant[11,12]. This bleeding risk is only increasing in significance as LVAD utilization gains acceptance and becomes more widespread with an effective rise in the prevalence. Recent discussions have focused on multidisciplinary approach to anticipation, timely diagnosis, and protocoled management of LVAD patient group[11,13,14]. In this latest review we discuss history of the LVADs, pathophysiology of GIB in LVAD recipients, clinical presentation, risk factors, location within the GI tract, differential diagnosis, management, and prognosis for these patients.

HISTORY

The first ventricular assist device (VAD) was used in 1966 by Michael DeBakey to help wean a woman from the heart-lung bypass machine (of his own design) after cardiac surgery[15]. Early LVADs were large and extracorporeal[16]. Mimicking normal ventricular function, they propelled blood in a pulsatile manner via pneumatic pressure pumps. Technological advances during the last quarter of the 20th century allowed for internalization of devices and a transition to electrical power.

Originally used to assist with myocardial recovery after infarction, LVADS were subsequently approved by the Food and Drug Administration (FDA) as a bridge to cardiac transplant[17]. Despite numerous complications, pulsatile LVADS only gained widespread use after the REMATCH trial in 2001[18]. Shown to prolong life in patients with end-stage heart failure[18], pulsatile LVADs posed a high thrombosis risk with early trials demonstrating a stroke rate as high as 16%[19] and a 50% greater infection rate than continuous-flow devices[8]. Intra-device stasis associated with pulsatility was thought to account for the elevated clotting and infection rates, leading to the development of a continuous flow model (CF-LVAD). Such devices use constant axial-flow through a rotary turbine to pump blood between the left ventricle and the aorta. Several models include Heartmate II (HMII) Left Ventricular Assist System (Thoratec)[20], the MicroMedDeBakey Ventricular Assist Device (MicroMed)[21], the Jarvik 2000 Heart (Jarvik Heart)[22], and the VentrAssist Left Ventricular Assist System (Ventracor)[23].

PATHOPHYSIOLOGY

The risk of bleeding in the setting of CF-LVAD is typically multifactorial - likely due to a combination of exogenous factors (anticoagulation and antiplatelet therapy), endogenous causes (fibrinolysis), intrinsic properties of the machines [the effect of the LVAD on endothelium, platelets, von Willebrand Factor (vWF), and angiogenesis], and the pre-disposing systemic conditions in the patients requiring such devices (hepatic and renal dysfunction).

Biomaterials and device structure

Hematologic responses to biomaterials and their effective interaction with blood components are important factors in augmentation of safe utilization of LVADs over the course of their development and clinical implementation. With significant clinical advances in its mechanical function, LVAD synthetic material

interaction with blood (including effective changes in its immunologic, inflammatory, and hematologic function) has come to spotlight as key concept in decreasing LVAD associated morbidity. To date, LVADs continue to impact expression of a variety of molecules in the coagulation and endothelial systems, including pro-thrombotic and pro-inflammatory intercellular adhesion molecule, E-selectin, and tissue factor[24]. As a result, new devices rely on materials with higher rate of hemocompatability, including titanium, acrylics, and polytetrafluoroethylene and additional optimization of LVAD surface continues to be a focus of both clinical and bench research.

Use of biomaterials and a technological advance away from the pulsatile LVAD systems have effectively decreased the risk of pump thrombosis, however, did not fully eliminate it. Sheer forces of the CF-LVAD change platelet shape and upregulate adhesion factors, which may lead to platelet activation, inducing aggregation and promoting adhesion to the endothelium and the device[25]. CF-LVADs are associated with a 6 per 100 patient-years stroke risk[8], a number comparable to advanced heart failure with atrial fibrillation[26], and a 6% overall thromboembolic event rate[27]. CF-LVAD patients remain on anti-platelet (aspirin or dipyridamole) and anticoagulation (warfarin) medications with a goal international normalized ratio (INR) of 1.5-2.5 immediately post-implantation and for duration of support to decrease the chance of thromboembolic event[28,29].

Early analysis did not demonstrate an increased risk of bleeding with LVAD to be greater than the baseline risk associated with concomitant aspirin and warfarin use[30,31]. However, more recent reviews have shown bleeding rates as high as 40% in HMII patients[32,33]. Additional studies provided further evidence that use of CF-LVAD confers a greater bleeding risk than pulsatile devices. Crow *et al*[34] found a tenfold increase in bleeding episodes per 100 person-years in CF-LVADs compared to pulsatile flow LVADs. A large retrospective review found that the odds of GIB were 3.24 times greater (95%CI: 1.53-6.89) in CF-LVAD recipients[4]. The risk further increases with age: in patients over 65 years old adjusted odds of GIB was 20.5 times greater (95%CI: 2.24-1.88) in continuous flow compared to pulsatile devices[4].

Anticoagulation

Use of antiplatelets and anticoagulants together increases the risk of bleeding above the risk associated with either agent alone and patients with LVAD are maintained on dual therapy for duration of the support. Initial experience with LVAD patients required higher degree of anticoagulation with warfarin but subsequent studies allowed for safe decrease of INR to 1.5-2.5 range without significant compromise in thromboembolic outcome[35]. Low level of auto-anticoagulation exists in advanced heart failure patients, both pre- and post-LVAD implantation[36]. Previous reports suggest a possibility of a specific genetic predisposition to both bleeding and clotting for LVAD patients, the exact mechanism of which is not entirely understood. Warfarin sensitive patients with rare polymorphisms in CYP2C9 (responsible for warfarin metabolism) and vitamin K epoxide reductase complex, subunit 1 (VKORC1) (protein inhibited by warfarin) may have paradoxical increase in both bleeding and thrombosis complications after LVAD placement[37] and additional studies are necessary to elucidate this hypothesis further.

Platelets

While aspirin or dipyridamole impair platelet function, the abnormalities seen in LVAD patients are not solely explained by medication use. Impaired platelet aggregation is partially caused by the interactions with artificial material and turbulent blood flow through the LVAD[35]. Platelets tend to exhibit an increased sensitivity to sheer stress, lysing at velocities far below speeds that would affect erythrocytes[38]. *In vitro*, blood circulated through the centrifugal pump of a VAD caused significant platelet injury[39]. *In vivo*, the MicroMedDeBakey VAD was shown to increase levels of platelet damage markers, platelet-factor 4 (PF4) and beta thromboglobulin β-TG (β-TG)[40], a concept resulting in impaired aggregation and adherence.

A recent study showed that many platelet abnormalities precede LVAD implantation. Patients with New York Heart Association class IV heart failure requiring LVAD placement typically exhibit multisystem dysfunction. Impaired ristocetin-induced platelet aggregation may be present in majority of LVAD recipients and normalizes after heart transplant[41]. Decreased hepatorenal perfusion results in decreased thrombopoetin production and uremia[42,43]. A cohort study of 112 LVAD patients showed that renal dysfunction correlated with increased incidence of GIB. The same study showed that ventricular failure was strongly associated with increased bleeding[13]. This can be explained by the augmented vascular resistance found in heart failure patients that leads to stasis and causes platelets to become hypersensitive and readily degranulate. Such platelets aggregate in a loose manner, are easily broken up by the sheer forces of blood flow and released back into the circulation dysfunctional[44]. Interestingly, there seems to be no difference in platelet aggregometry in patients with LVAD compared to their own blood prior to LVAD implantation, a result with important implications[44]. Indeed, while normalization in perfusion parameters and end organ function may improve after LVAD placement, the device use itself may result in additional burden on platelet function.

Fibrinolysis

Previous studies have indicated an augmented acti-

vation of fibrinolytic systems in older end stage heart failure patients prior to undergoing LVAD implant for destination therapy, likely a result of pre-existing state of inflammation[45]. It has been shown that baseline fibrinogen and d-dimer levels peak at one month and subsequently return to almost normal levels by one year post-implantation[36]. It is possible that early rise in fibrinolysis is related to the initial biomaterial contact with blood protein. Studies have revealed that the majority of bleeding events occur during the first year after LVAD placement, well within this coagulopathic time frame[11]. Further analysis is necessary to better evaluate additional factors in fibrinolytic triggering mechanism of heart failure patients both pre- and post- LVAD implantation.

Acquired von willebrand syndrome

Perhaps one of the more important aspects in understanding propensity to bleed in LVAD recipients is the development of acquired von Willebrand syndrome (avWs). Physiologically, vWF is made in the endothelial cells, released into the bloodstream as a high molecular weight (HMW) multimer that bind factor Ⅷ and plays an important role in hemostasis. It is cleaved by ADAMTS-13, glycosylated and cleared from the bloodstream with a half-life of 12-20 h[46]. Effective hemostasis relies on the proper balance between its production and elimination[47]. However, mechanical forces of LVAD device can easily shear and deform the HMW multimers into smaller, medium and low molecular weight fragments, which impairs thrombosis and interferes with platelet aggregation[41]. In a study of 37 LVAD patients, all subjects showed significant loss of high molecular weight vWFmultimers within 30 d of CF-LVAD placement[48]. vWF multimers and platelet aggregation are significantly reduced in all LVAD recepients but return to normal post-explantation[49]. Importantly, recent analysis with enzyme-linked immunosorbent assay revealed that the LVAD-induced proteolysis is speed dependent[50], resulting in important implications on LVADs setting and bleeding risk and potentially providing an opportunity to regulate hemostasis on individual basis. Finally, normal vWF multimers play an important role in platelet-induced hemostasis as blood flows through angiodysplasias and vWF defragmentation may by itself be pro-angiogenic, an important concept in potential explanation of gastrointestinal hemorrhage in LVAD patients[35,51].

Vascular abnormalities

Finally, most important factor in development of GIB in LVAD patients remains presence of old or development of new gastrointestinal lesion. While existing gastrointestinal pathology may increase likelihood of bleeding, the LVAD placement put patients at risk of angiodysplasia formation in the upper gastrointestinal tract. CF-LVADS create a direct connection between the left ventricle and the aorta bypassing the aortic valve[52]. Similar to the hemodynamic changes in severe aortic stenosis, described by Edward C. Heyde in 1958[53], the continuous flow state of the LVADs create chronic narrow pulse pressure system altering neurovascular physiology, increasing sympathetic tone, intraluminal pressure, and smooth muscle relaxation with resultant distention of submucosal venous plexus and angioectasia formation[54]. Vascular anomalies have also been shown in selected animal studies[55]. Apparent predilection of bleeding angioectasias to the upper gastrointestinal tract may be related to the close proximity of the celiac axis and proximal jejuna branches of the proximal superior mesenteric artery to the LVAD and thus receiving more effective stress compared to distal gastrointestinal vasculature. In addition, chronic low flow state observed in congestive heart failure patients places their capillary systems at the state of equilibrium which is offset immediately by increased cardiac output seen after LVAD implantation[13].

Occult NSAID and other medication use

Many LVAD recipients are elderly and the devices function as destination therapy rather than as a bridge to transplantation. These patients may be concurrently taking over-the counter non-steroidal anti-inflammatory medications (NSAIDs) for other causes, such as arthralgias and arthritis. NSAID use if often not screened for and, as shown in a cross-sectional survey of emergency room departments in the United States, only 58% of the patients are aware of NSAID side effects, with 48% believing that the medications are entirely safe[56]. Polypharmacy is a frequently seen phenomenon in elderly and morbid patients, placing them at risk of drug-drug interaction and additional effects on hemostasis. Common medications used in patients with advanced heart failure and LVAD placement include b-blockers, ACE-inhibitors and calcium channel blockers - all of which may affect platelet function and aggregation[44].

CLINICAL PRESENTATION AND RISK FACTORS

Gastrointestinal hemorrhage in patients with LVAD presents similarly to general population including hematemesis, coffee-grounds emesis, melena, heme positive stools, and rectal bleeding. Patients may complain of worsening fatigue, weakness, lightheadedness, dizziness or show up entirely asymptomatic. Laboratory analysis may reveal worsening anemia, rise in international normalized ratio, decrease in platelet count, and increase in blood urea nitrogen compared to patient's baseline values. The average time to first presentation of GIB is close to 5 mo, but the clinician should be aware of early and late episodes that may occur immediately or long after

LVAD placement. Recurrent GIB is common and may not always follow the initial episode in time or type of presentation. Hemodynamic instability is uncommon but may occur. Male gender and older age may place patients at additional risk of bleeding following LVAD placement. Potential risk factors include history of pre-LVAD GIB, use of concomitant anti-platelet and vitamin K antagonist therapy, increased pump rotary speed, right ventricular dysfunction, and post-LVAD ejection fraction > 30%[9,11,13] - probably a combination of general predisposition, effective potentiation of hemorrhage, and altered neurovascular physiology in LVAD recipients. Additional variables are likely to emerge with time as we gain more insight into disease processes with increased utilization of LVADs in cardiology practice worldwide.

LOCATION IN THE GI TRACT AND DIFFERENTIAL DIAGNOSIS

Various studies have focused on identifying distribution of culprit lesion in the gastrointestinal tract in LVAD recipients. In fact, every part of the bowel may be affected but the majority of the bleeding seems to originate in the stomach, duodenum or jejunum. Over half of the offenders are angiodysplasias of which nearly 90% occur in the upper gastrointestinal tract with 25% of them affecting the jejunum[11]. Other causes may include hemorrhage from Dieulafoy lesions, peptic ulcer disease, bowel ischemia, radiation proctitis, neoplasia, diverticulosis, or hemorrhoids. It is important to realize that while LVAD patients have a propensity for developing angioectasia-associated bleeding from the upper GI tract or have another GI-related etiology of bleeding, the differential diagnosis of anemia in such patients should also embrace the non-gastrointestinal causes including nasal, retroperitoneal, genitourinary, mediastinal, prostate, intracranial bleeding, hemolysis, mineral deficiencies, or anemia related to renal insufficiency or chronic disease[11,12,36]. In fact, several conditions may co-exist and gastrointestinal bleeding may present as an acute drop in the hematocrit level from the baseline abnormal value.

MANAGEMENT

Approach to LVAD patients with gastrointestinal hemorrhage should be multidisciplinary and comprehensive. In the emergency room setting, patient should be immediately assessed and hemodynamically resuscitated. Detailed history and review of systems should be performed and special attention needs to be directed at the medical list including over-the-counter or herbal medications. NSAIDs use should be questioned as it may contribute to the cause of bleeding and is often under-reported by the patient. Physical examination including evaluation of LVAD function by cardiology team and consult to gastroenterology service should be completed in the emergency department. Intensive care admission should be assessed on an individual basis. Urgent bloodwork should include complete blood count, metabolic and hepatic panels, INR, fibrinogen, and a d-dimer assay. Holding of the antiplatelet and anticoagulation therapy with consideration of platelet and/or fresh frozen plasma transfusion should be discussed with cardiology service, weighing in risk of thrombosis. Correction of blood abnormalities, including packed red blood cell transfusion should be performed in patients with significant anemia or signs of hemodynamic compromise. Endoscopic management of the GIB in LVAD patients remains a cornerstone in both identifying the source of hemorrhage and effectively intervening on it to stop the bleeding. Importantly, it should be performed with assistance of cardiac anesthesiologist or a general anesthesiologist trained in LVAD patient management. Known predilection to the upper gastrointestinal tract together with clinical presentation and stool analysis provide gastroenterologist an initial clue to the location of bleeding. Colonoscopy has limited role in evaluation for cause of GIB in patients with LVAD[51] but should be performed for colon cancer screening in age appropriate group according to standard guidelines[57]. With the exception of frank rectal bleeding with hemodynamic stability where a colonoscopy may be the initial approach, upper gastrointestinal endoscopy is always warranted. However, esophagogastroduodenoscopy is non-diagnostic in over two thirds of the patients[11,32]. Patients with melena or hematochezia associated brisk upper gastrointestinal hemorrhage and suspected small intestinal angiodysplastic lesion would require a push enteroscopy to evaluate proximal jejunum. In fact, routine use of push enteroscopy increased diagnostic and therefore therapeutic yield from 29% to 90% in LVAD patients with gastrointestinal hemorrhage and may decrease future GI readmission rates[11,32]. Deep balloon assisted enteroscopy or small bowel video capsule endoscopy may be necessary in the remaining cases. In fact, video capsule (while safe in LVAD patients) may aid in detection of bleeding in up to 40% of the cases, with majority localized in the proximal small bowel[58], although a follow up endoscopic intervention would still be warranted. Easy to perform and well tolerated, capsule endoscopy is not therapeutic, may delay immediate diagnosis, and result in increase in hospital stay[58]. Early use of deep balloon assisted enteroscopy, on the other hand, may decrease transfusion requirements, length and cost of hospitalization, but is cumbersome, riskier, and more invasive that traditional push enteroscopy[59-61]. It may provide additional benefit in cases of suspected hemorrhage in LVAD patients beyond proximal to mid jejunum[11,59]. Endoluminal intervention is directed at the culprit lesion, and given high incidence of

small intestinal angiodysplasias, various hemostatic tools may be employed including argon plasma coagulation alone or in combination with resolution clips/submucosal racemic epinephrine injection[11,62,63]. In fact, utilization of LVAD specific GIB algorithm on institutional basis may provide structured approach to effective management of this patient population and ultimately improve clinical outcome[11].

Discharge planning of LVAD patients with GIB should focus on secondary prevention of future hemorrhages. In fact, up to half of the patients presenting with their first hemorrhage may return to the hospital with recurrent GIB approximately 100 d after initial admission[11] and repeat endoluminal intervention may be warranted. Multidisciplinary approach with risk stratification involving cardiology, hematology, and gastroenterology services may discuss potential alterations in antiplatelet and anticoagulation therapies or adjustment of the LVAD pump speed[13,35]. On a case by case basis, success with octreotide - a somatostatin analogue which acts as a splanchnic vasoconstrictor and may affect angiogenesis - has been reported[64], but its application to control bleeding and prevent future hemorrhages in LVAD patients may be offset by high cost and limited outpatient use[11]. Recent small phase I trial showed octreotide potential effectiveness and general tolerability as early intervention[65] and future large prospective randomized investigations would be necessary to further define its role in LVAD population. There was anecdotal use of antihemophilic factor/vWF complex and hormonal (estrogen, desmopressin) therapy in refractory bleeding[35,66], although unclear if the patient would have benefited from repeated small intestinal evaluation prior to its initiation. Importantly, desmopressin use, while increasing circulating vWF, places the patient at risk of thrombosis[67]. Of interest, blood type A patients may exhibit lowest risk of bleeding[48], an factor that may play a role in risk-stratification of LVAD patients. Possible correlation to GIB may be found in patients with increased nasal hypervascularity after LVAD implantation[68] and may be potentially used to help risk stratify patients. Future research may provide additional insight into management of such patients, perhaps focusing on further definition of various parameters in individual anticoagulation therapy and recognizing patients with highest risk for bleeding at the time of LVAD implant. Primary prevention strategies therefore may come into play with potential pre-LVAD gastrointestinal and hematologic screening.

PROGNOSIS

GIB in LVAD recipients increases overall patient mortality compared to non-bleeders[13] and places additional burden on cost of care[11]. Rebleeding rate may be seen close to 50% in the literature[46,51]. Early jejunal intubation with push enteroscopy significantly increases the yield of detection and correction of angiodysplastic bleeding with four fifths decrease in GIB related hospital readmissions[11] but additional long term studies are required. Recent advances in understanding of pathophysiology, risk factor recognition, etiology, and timely intervention are expected to improve overall prognosis in LVAD GIB patients. Ultimately, cessation of GIB is seen in all patients after cardiac transplantation, likely a reflection of normalization of previously LVAD-induced hematologic and hemodynamic parameters.

CONCLUSION

As CF-LVADS have replaced pulsatile devices, overall outcomes have improved. However, the incidence of gastrointestinal bleeding has increased significantly and hemorrhage remains major concern in patients receiving LVAD placement for end stage congestive heart failure, resulting in rise of hospital admissions, procedure burden, and cost[4,11]. Etiology is multifactorial, a combination of post-operative use of blood thinners, activation of fibrinolytic pathway, acquired vWF deficiency, and device related upper gastrointestinal angiodysplasia formation. Multispecialty approach with individual risk stratification and tailored therapy plays an important role in managing this patient population. Algorithmic endoscopic approach with gastroduodenojejunal evaluation is crucial in hospitalized patients. Future long term randomized studies are necessary and should focus on primary and secondary prevention of GIB in LVAD patients without compromising device function and pump related non-GI complications.

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