GASTROINTESTINAL BLEEDING AFTER CONTINUOUS-FLOW LEFT VENTRICULAR DEVICE IMPLANTATION: REVIEW OF PATHOPHYSIOLOGY AND MANAGEMENT

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Abstract

Gastrointestinal bleeding is one of the most common complications in patients with continuous-flow left ventricular assist devices. Though the exact pathophysiology is still unclear, continuous-flow physiology, acquired Von Willebrand disease, and formation of arteriovenous malformations in the gastrointestinal tract are implicated. An individualized plan of endoscopic therapy and anticoagulation management is required when caring for these patients.

Introduction

An increasing number of patients with end-stage heart failure are being implanted with continuous-flow left ventricular assist devices (CF-LVADs). According to the 2014 Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) report, 3,500 CF-LVADs were implanted in 2013, and this number is expected to grow.[1] Gastrointestinal (GI) bleeding is one of the most common complications seen in patients on device support. We review the incidence, pathophysiology, and management algorithm of GI bleeding in patients with CF-LVADS.

The incidence of GI bleeding in patients with CF-LVADS is between 18.9% and 22.3%.[2] This is considerably higher compared to the earlier-era pulsatile LVADs, where the incidence was about 10%. Gastrointestinal rebleeding rates are about 35%, with a mean of 1.5 ± 0.2 recurrent bleeding events per patient.[3] The cause of bleeding is found in about 75% of the patients. Of those who rebleed, about 75% have similar symptoms, and etiology of rebleeding is the same as the index bleeding episode in 50% of the patients. The anatomic location of bleeding is predominantly upper GI in origin, and most of them are from angiodysplastic lesions (Table 1).

Pathophysiology of GI Bleeding

Gastrointestinal bleeding in patients with CF-LVADS stems from a combination of factors including therapeutic anticoagulation and continuous-flow physiology, which leads to acquired Von Willebrand disease, impairment of platelet aggregation, and formation of arteriovenous malformations in the GI tract. Patients on CF-LVAD support require anticoagulation with warfarin and aspirin, whereas those on pulsatile LVADs require only aspirin. Even so, the event rate of GI bleeding in patients with CF-LVADs is much higher—65 per 100 patient years compared to 2.60-4.6 per 100 patient years in patients with mechanical valves (on aspirin and warfarin), and 8% in patients receiving triple antithrombotic therapy (aspirin, clopidogrel, and warfarin).[4,5] Furthermore, nearly all patients with assist devices who experienced GI bleeding had therapeutic or subtherapeutic international normalized ratios (INRs) at the time of their bleeding events,[5-7] suggesting that antithrombotic therapy alone does not account for the higher bleeding rate in patients with CF-LVADS. Pulsatile LVADs that were used prior to the advent of CF-LVADs had a lesser incidence of GI bleeding (10%), initially suggesting that there may be a relationship between pulsatility and bleeding.[3] It has been hypothesized that physiologic changes related to a lack of pulsatility account for the increased rate of GI bleeding in patients on continuous-flow pumps.

Acquired von Willebrand syndrome was first described to explain GI bleeding in patients with severe aortic stenosis and Heyde's syndrome.[8] It was believed that the high shear stress and lack of pulsatility induced loss of high-molecular-weight von Willebrand multimers, leading to increased bleeding. Similarly, multiple centers have demonstrated significantly decreased or absent high-molecular-weight multimers in all patients with a

	Total Incidence	Gastritis	Gastric Ulcer	AVM	Diverticulitis	Colitis	Colonic Polyp	Colonic Ulcer	Other	Unknown
Hayes et al.	13.9%			60.0%				20.0%		20.0%
Demirozu et al.	19.0%	31.3%		31.3%	18.8%	3.2%	3.2%		12.5%	
Aggarwal et al.	22.8%	30.4%	8.7%	21.7%			4.3%	13.0%	13.0%	8.7%
Kushnir et al.	34.8%		28.2%	30.8%		5.1%	5.1%			30.8%
Wever-Pinzon et al.	17.2%	8.7%		61.0%	8.7%	4.3%	8.7%		8.7%	
*AVM = Arteriovenous malformation										

Table 1. Summary of all studies that identify the source of bleeding.

variety of CF-LVADs.[7,9,10] Crow et al. compared levels of high-molecular-weight multimers in patients pre- and post-LVAD implantation with both pulsatile and continuous-flow devices. All patients with CF-LVADs had an absence of high-molecular-weight multimers, whereas the levels were normal in patients who received pulsatile LVADs. Studies that examined patients who underwent explantation of their CF-LVAD due to transplantation or myocardial recovery showed 100% reversal of the von Willebrand deficiency.[7,10]

In addition to the loss of large-molecular-weight von Willebrand multimers, impaired platelet aggregation has also been proposed as a mechanism for increased GI bleeding post-LVAD implant. Klovaite et al. studied platelet aggregation in 16 patients after CF- LVAD and found that ADP-induced platelet aggregation was reduced in seven patients (44%), of whom only two were taking aspirin.[9] Five patients with abnormal platelet aggregation experienced normal platelet aggregation after undergoing heart transplantation, suggesting that the ventricular assist device was a causative mechanism in the abnormal aggregation.[9]

Given the high prevalence of platelet abnormalities (up to 75% in some studies) and deficiency of von Willebrand multimers of CF-LVAD patients, these findings alone cannot explain the increased rate of GI bleeding. In studies evaluating outcomes in patients with CF-VADs, arteriovenous malformations (AVMs) accounted for up to 61% of GI bleeding.[6] Several studies looking at risk factors for GI bleeding have shown that the majority of patients with continuous-flow devices who develop GI bleeding have no prior history of bleeding,[4,5] and a recent meta-analysis demonstrated that a prior history of GI bleeding was not a risk factor for bleeding post-VAD implantation.[11]

In a study examining the relationship between pulsatility index and post-surgical bleeding in patients with continuous-flow HeartMate II devices, Wever-Pinzon et al. found a significant association between a low pulsatility index and the risk of bleeding from AVMs.[6] Cappell and Lebwohl suggest that increased sympathetic tone in a low pulsatile state leads to smooth muscle dilation and consequently arteriovenous dilation.[12] Animal studies have demonstrated that continuous-flow physiology leads to microvascular hypoperfusion, even if a physiological mean blood pressure is maintained, and this is believed to lead to localized hypoxia, vascular dilatation, and angiodysplasia as well.[2]

Diagnostic Algorithm

The diagnostic algorithm for GI bleeding in patients with a CF-LVAD should be similar to the diagnostic algorithm of all patients with GI bleeds, with several caveats (Figure 1A). CF- LVAD recipients generally have several severe comorbid diseases; therefore, if GI bleeding is suspected in these patients, there should be a low threshold for admission and inpatient workup.[13] The diagnostic algorithm for patients with GI bleeding involves timely assessment of the nature, location, and time course of the bleeding episode.

The history and physical exam should suggest the initial site of bleeding. Reviewing medications, especially any over the counter medications, is imperative since NSAID use increases the risk of bleeding even without aspirin. Patients with hematemesis or melena should be considered to have upper GI bleeding. The American College of Gastroenterology guidelines recommend that patients with suspected upper GI bleeding should undergo upper endoscopy, after appropriate resuscitation, within the first 24 hours of hospital admission.[13] Nasogastric (NG) lavage may be considered initially for evaluation of those patients suspected of having an upper GI bleed. Of patients with a bloody aspirate on NG lavage, 45% will have a high-risk lesion found on endoscopy

versus 15% of those with a clear or bilious aspirate. The odds of a high-risk lesion are 2.69-times higher among those who have a positive NG lavage finding verses those with a negative NG lavage finding. NG lavage aspiration risk in the setting of LVAD bleeding is usually minimal. If there is profuse bleeding or the patient is unstable, the patient's airway should be protected with prophylactic intubation. However, performance of NG lavage has been shown to have no benefit with respect to medical outcomes.[14] Intravenous erythromycin (3 mg/kg over 20-30 min) given 30 to 90 minutes prior to endoscopy enhances clearing of blood, clots, and possible food residue in the stomach.[15]

In patients with CF-LVADs who are on warfarin and aspirin, performing procedures to stop the bleeding can be challenging as they often require cauterization. It has been our center's practice to stop aspirin and warfarin and wait until the INR is less than 1.5 to perform the procedure. However, this may interfere with diagnostic yield since occult bleeding may cease when the INR is corrected. Studies have shown that performing an upper endoscopy with an elevated INR between 1.3 and 2.7 is not associated with an increased risk of rebleeding, transfusion requirement, surgery, or mortality.[16] If there is ongoing GI bleeding with clinical instability, the procedure must be performed irrespective of the INR.

Patients with clear clinical stability and hematochezia or long history of intermittent hematochezia can be investigated for suspected lower GI bleeding, with the initial examination being colonoscopy after adequate bowel prep. If colonoscopy in this circumstance is unrevealing, then esophagogastroduodenoscopy (EGD) should be the next evaluation.[17] If initial EGD and colonoscopy do not indicate localization of the bleeding site, then the patient is said to have obscure GI bleeding.[18] A variety of modalities exist to evaluate obscure GI bleeding, and the clinical scenario should continue to define which modality is chosen as the next best test following the initial EGD and colonoscopy (Figure 1 B, C). Current examinations include video capsule endoscopy (VCE), push enteroscopy, deep balloon-assisted enteroscopy, nuclear red blood cell scintigraphy, and angiography. All these modalities have been studied in the CF-LVAD population and found to be safe—causing no interference with LVAD functioning. CF-LVAD patients with obscure occult GI bleeding or inactive obscure overt GI bleeding should undergo video capsule endoscopy (*VCE*) to help localize a bleeding site, as VCE is more effective at discovering clinically significant lesions (56%) than push enteroscopy (26%) or small bowel follow-through (6%).[19] Furthermore, VCE has been shown to detect more bleeding source lesions than CT and standard angiography (72% vs. 24% and 56%, respectively).[20] The frequency of AVM-related bleeding in CF-LVAD patients makes VCE localization a valuable tool in guiding deep enteroscopy and thermal treatment of these lesions. Active overt GI bleeding may also be evaluated with tagged red blood cell (RBC) scan or angiography, depending on the clinical interpretation of the bleeding rate (bleeding rate must be at least 0.1- 0.5 cc/min or > 0.5 mL/m, respectively). A focal volume of 3 mL can regularly be detected by tagged RBC scan, but hyperactive peristalsis can reduce sensitivity[21] Lesions that are bleeding rapidly would benefit from angiography with the intention of angiographic intervention. Actively bleeding lesions in less critical patients can be quickly located with nuclear scintigraphy, which can also guide deep enteroscopy with therapeutic intent. VCE may still have a role in evaluating actively bleeding lesions, depending on the clinical stability of the patient, a low rate or intermittent activity of bleeding lesions, the availability of staff to arrange for and interpret the study, and the location of the patient at the time of the examination, as
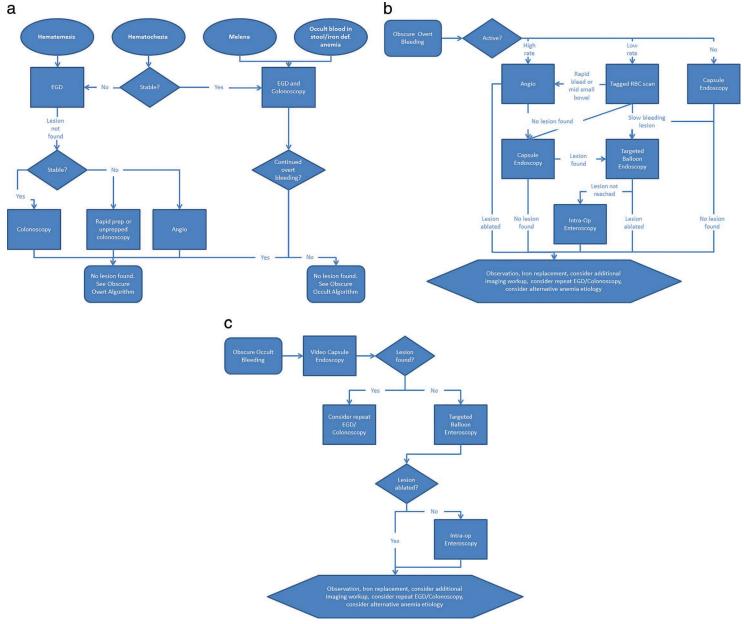
Figure 1. Diagnostic algorithms for (A) first episode of bleeding, (B) obscure overt bleeding, and (C) obscure occult bleeding.

VCE is often not available in the inpatient setting where CF-LVAD patients are being evaluated.

Rebleeding

Gastrointestinal rebleeding in patients with CF- LVADs is common and most likely occurs in the same site as the first bleeding episode.[3] Treatment decisions in an episode of rebleeding should be individualized based on the patient's history, including when the prior EGD and colonoscopy occurred, the type of lesion(s) previously found, and the clinical stability of the patient. Repeating an EGD, VCE, or colonoscopy is helpful, and missed lesions such as Cameron erosions, Dieulafoy's lesions, gastric antral vascular ectasias, and angioectasias are sometimes encountered within reach of standard endoscopes.

Management of Anticoagulation

No studies have investigated the optimal anticoagulation management in the cohort of patients with CF-LVADs and GI bleeding. At our center, the anticoagulation strategy is based on the number of GI bleeding episodes, the INR at the time of GI bleeding, and concomitant comorbidities that require antiplatelet or therapeutic anticoagulation such as stroke and atrial fibrillation (Table 2).

Interventions to Reduce Formation and Bleeding from AVMs

There are case reports about successfully using octreotide to treat acute GI bleeding and continuing it as an outpatient therapy to reduce GI bleeding in patients with CF-LVADs. Similarly, thalidomide has been used to decrease the formation of AVMs due to its antivascular proliferative effect. However, the increased risk of thrombosis with thalidomide has to be balanced with its putative beneficial effect.[2,11] Neither of these drugs have been systematically studied in the CF-LVAD population but may be considered in patients with refractory bleeding.

Number of GI Bleeding Episodes	Anticoagulation and Antiplatelet Strategy
First Episode	Decrease INR goal to 1.5-1.8
	Continue aspirin
Second Episode	Continue warfarin with INR goal of 1.5-1.8
	Discontinue aspirin
Third Episode	Decrease INR goal to 1.0-1.5
Fourth Episode	Discontinue warfarin
	Consider adding reduced dose enoxaparin (0.5mg/kg/day)
Fifth Episode	Discontinue all anticoagulation

Table 2. Houston Methodist Hospital's strategy for management of anticoagulation in patients with recurrent rebleeding episodes.

Reintroducing Pulsatility to Decrease the Risk of AVM Formation

Though there are studies demonstrating that decreased pulsatility is associated with AVM formations, there are no systematic studies showing that increasing pulsatility will decrease the risk of recurrent GI bleeding.[6] However, the practice at our and other centers has been to provide better pulsatility by decreasing pump speed after a GI bleeding episode, particularly one from an AVM. The theoretical benefit of decreasing pump speed must be balanced with risk of inadequately unloading the patient and precipitating heart failure.

Conclusion

Gastrointestinal bleeding is one of the most common problems in patients with long-term CF-LVAD support. It often leads to significant morbidity that results in multiple readmissions. A multidisciplinary team approach is required for every patient to individualize treatment decision-making with regard to gastrointestinal procedure and anticoagulation therapy.

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