Advances in Heart Failure

Mechanisms of Bleeding and Approach to Patients With Axial-Flow Left Ventricular Assist Devices

Jorge Suarez, BS; Chetan B. Patel, MD; G. Michael Felker, MD; Richard Becker, MD; Adrian F. Hernandez, MD, MHS; Joseph G. Rogers, MD

During the past several decades, left ventricular assist devices (LVADs) have become a valuable therapeutic option in the management of advanced systolic heart failure. Durable LVADs are being used to provide long-term mechanical circulatory support to a growing population of patients with end-stage systolic heart failure refractory to medical and electric therapies. This advanced stage of heart failure is associated with unacceptably high mortality when treated with medical therapy alone, and these patients are traditionally referred for cardiac transplantation.1,2 Unfortunately, the number of heart transplantations performed in the United States is limited by the availability of donor organs to approximately 2200 per year, a small fraction of the total patients requiring advanced heart failure care.3 Moreover, 75% of patients with end-stage heart failure are >65 years and have severe comorbid conditions, making them ineligible for transplantation at many centers.4

As a result of innovative trials, LVADs have become a therapeutic option in patients with end-stage heart failure as bridge-to-transplantation or destination therapy in patients deemed ineligible for cardiac transplantation.5,6 Contemporary LVADs are continuous-flow pumps that allow for smaller pump size and improved mechanical reliability and durability.7 In a landmark study8 comparing the HeartMate XVE, an older generation pulsatile pump (Thoratec Corp; Pleasanton, CA), with the newer HeartMate II LVAD (Thoratec Corp), the continuous-flow pump outperformed the pulsatile device in overall survival, pump failure events, and infectious complications. Device technology continues to improve, and third-generation continuous-flow LVADs under development use magnetic or hydrodynamic bearings for frictionless rotation of the rotor that may further enhance durability.9

One potential limitation of continuous-flow pump technology is the relatively high nonphysiological shear stress imparted on blood components as they move through the device. This stress, coupled with the reduced pulse pressure associated with axial-flow LVADs, may cause unanticipated increases in nonsurgical bleeding events secondary to arteriovenous malformations (AVMs) in the gastrointestinal (GI) tract and the development of acquired von Willebrand disease. Bleeding, especially from a GI tract source, has recently been identified as 1 of the most common adverse events after implantation and is a major cause of morbidity in patients supported by LVAD therapy.10–13 Fortunately, there have been no documented increases in mortality associated with these increased rates of GI tract bleeding. With the requirement for systemic anticoagulation after implantation of contemporary LVADs, an advanced understanding of the mechanisms underlying these bleeding risks is necessary to guide postimplantation management and therapy. In this review, we summarize the literature evaluating the prevalence, etiology, outcomes, and management of bleeding events in the LVAD population. We also identify areas where more studies are necessary to guide future therapies and interventions. Our comments will primarily focus on the population of patients treated with axial-flow devices, such as the US Food and Drug Administration–approved HeartMate II, which propels blood continuously along the axis of a helical rotor known as an impeller. The limited experience with newer continuous-flow pumps that use a centrifugal flow mechanism requiring lower revolutions per minute does not permit extrapolation of these comments to all continuous-flow pumps.

Bleeding Events in Axial-Flow LVADs

Incidence

Recent data suggest that 1 of the most common adverse events within the first 30 days after LVAD implantation is nonsurgical bleeding.7,10,12,14–16 The Table summarizes the reported bleeding events in studies that included patients treated with an axial-flow LVAD. In a multicenter study14 demonstrating the effectiveness of the HeartMate II axial-flow LVAD in patients awaiting a heart transplantation, the most common adverse event within 30 days of implantation was nonsurgical bleeding, resulting in surgery or significant blood transfusions. Across studies, the most commonly reported sources of bleeding are epistaxis, GI tract bleeding, bleeding of the mediastinum and thorax, and intracranial hemorrhage.7,12,14 Data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) have shown the most frequent locations of first bleeding episode after implantation to be mediastinal (45%), thoracic pleural space (12%), lower GI tract (10%), chest wall (8%),
and upper GI tract (8%), with no difference in the overall bleeding rates between axial- and pulsatile-flow devices.\(^{18}\) However, the location of bleeding may vary depending on time from operation, with thoracic or mediastinal bleeding having higher, but diminishing, risk in the early postoperative period, with a delayed risk of GI tract bleeding. In a smaller study\(^{19}\) of 48 patients who underwent transplantation with an axial-flow device, GI tract bleeding appeared late after implantation, with an average of 460 days of ventricular support. Small retrospective analyses\(^{10,16}\) have shown significantly increased rates of GI tract bleeding with the use of axial-flow devices when compared with pulsatile-flow devices, which may be related to rates of readmission for axial-flow devices. Indeed, the INTERMACS data have also shown axial-flow devices to have overall decreased rates of bleeding compared with pulsatile-flow devices, when readmissions due to bleeding (9.8%) are compared with axial-flow devices.\(^{20}\) Therefore, the increased observed rates of bleeding in patients treated with axial flow LVADs were higher than would be expected from anticoagulation therapy alone. In fact, with current rates of GI tract and intracranial bleeding reported as high as 30% and 11%, respectively,\(^{7,21}\) analyses\(^{7,21}\) have suggested that the risk of bleeding is greater than that of thromboembolism. This has led to center-specific changes in anticoagulation management after both implantation and a bleeding event (Figure 1), with a shift to a decrease in target international normalized ratio (INR) at many centers.\(^{8}\) For instance, to reduce GI tract bleeding risk in these patients, the Henry Ford Hospital (Detroit, Mich) has lowered the anticoagulation target to an INR of 1.8 to 2.2, with no increase in thromboembolic complications.\(^{15}\) Although there have been no reports of increased thrombosis or embolic stroke events from other centers modifying their anticoagulation regimen, this has been a recent change in practice and we await longer-term follow-up. Additional efforts have also been undertaken to understand the mechanisms associated with heightened bleeding risk after the implantation of axial-flow devices. Angiodysplasia, impaired platelet aggregation, and a newly identified acquired von Willebrand disease have all been proposed as possible mechanisms responsible for these observations.\(^{22}\)

### Table. Reported Bleeding Events in Axial-Flow LVADs

<table>
<thead>
<tr>
<th>Source</th>
<th>Rate of Adverse Event, %</th>
<th>Definition of Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>All bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pagani et al,(^{14}) 2009</td>
<td>26</td>
<td>Requiring surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Requiring (\geq 2) PRBCs</td>
</tr>
<tr>
<td>Slaughter et al,(^{7}) 2009</td>
<td>30</td>
<td>Requiring surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Requiring PRBCs</td>
</tr>
<tr>
<td>Pal et al,(^{15}) 2009</td>
<td>9</td>
<td>Requiring surgery</td>
</tr>
<tr>
<td>GI tract bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crow et al,(^{10}) 2009</td>
<td>21.8</td>
<td>All bleeding events that occurred past postoperative day 15</td>
</tr>
<tr>
<td>Genovese et al,(^{12}) 2009</td>
<td>5.1</td>
<td>Cumulative incidence by 60 d after implantation</td>
</tr>
<tr>
<td>Uriel et al,(^{16}) 2010</td>
<td>30</td>
<td>Any nonsurgical bleeding requiring transfusion</td>
</tr>
<tr>
<td>Crow et al,(^{17}) 2010</td>
<td>13.5</td>
<td>Bleeding requiring any type of intervention</td>
</tr>
</tbody>
</table>

PRBC indicates packed red blood cell.

Acquired von Willebrand Disease With Axial-Flow LVADs

The von Willebrand factor (vWF) molecule is a 250-kDa protein expressed by vascular endothelial cells that assembles into multimers that bind to exposed collagen of damaged blood vessels. It also binds to platelet receptors to induce activation, adhesion, and aggregation.\(^{22}\) Homeostasis of the vWF multimer size is necessary to prevent a pathological
coagulopathy and is primarily regulated by the cleavage activity of the metalloprotease ADAMTS13. ADAMTS13 is a protease that binds to and cleaves the vWF protein at a specific site (the A2 domain) that is buried in the tertiary structure of the protein until the molecule unfolds. A deficiency of this protease is responsible for large vWF multimers, which, in turn, are responsible for the development of the prothrombotic condition, thrombotic thrombocytopenic purpura.23 Conversely, excessive cleavage of large multimers results in vWF multimer depletion and pathological bleeding, as seen in acquired von Willebrand disease.

The relationship between the loss of high-molecular-weight (HMW) vWF multimers (acquired von Willebrand disease) and GI tract bleeding was first described in a phenomenon called Heyde syndrome. This syndrome affects individuals who have severe aortic stenosis and concomitantly develop a combination of acquired von Willebrand disease and GI tract bleeding.24 Multiple mechanisms have been proposed for the development of this syndrome. One potential explanation for the acquired von Willebrand disease invokes high shear stress across the calcified aortic valve, inducing a conformational change on the vWF multimers and predisposing them to proteolytic cleavage.10 Another contributing factor is increased intraluminal pressure within the vasculature and the lowered pulse pressure,22 which is discussed in detail later in this review. Because axial-flow LVAD physiological characteristics involve high shear stress and narrow pulse pressures, it is intriguing that patients treated with contemporary LVADs have bleeding patterns similar to those described with severe aortic stenosis.

Geisen et al11 compared blood samples from heart transplant recipients and patients treated with axial-flow LVADs to examine the role of impaired hemostasis after the initiation of continuous-flow therapy. Both groups had comparable prothrombin time, platelet count, and total vWF levels. A key difference in the LVAD population was the reduced number of HMW vWF multimers,11 an observation that has been replicated in multiple cohorts.16,17,24,25 Although consistent across studies, the mechanisms underlying the loss in HMW vWF are under intense investigation; at this time, they remain putative. A particular focus has been the impact of shear stress on vWF cleavage, a relationship defined experimentally by Tsai et al26 in 1994, well before the development of contemporary LVADs. By perfusing normal plasma through long capillary tubing, these investigators observed a direct relationship between the shear rate and the loss of HMW vWF multimers. They concluded that shear stress promoted vWF proteolysis by the metalloprotease ADAMTS13, leading to a decrease in multimer size.26 By using molecular simulation, Baldauf et al27 demonstrated that the high shear stress rates resulted in elongation and unfolding of the vWF multimers. Consequently, the enhanced exposure of the previously buried A2 domain results in the cleavage by the ADAMTS13 metalloprotease. As the shear stress rate increases, the molecule is prone to unfolding, resulting in greater cleavage rates and smaller vWF multimers.27

Multiple studies16,17,28 have shown that most patients who undergo implantation with an axial-flow LVAD will develop some degree of acquired von Willebrand disease. In a retrospective review16 of 79 patients with a HeartMate II LVAD, all patients had decreased or absent HMW vWF multimers that normalized after heart transplantation. Similar findings were reported in a multicenter study involving the Duke University Medical Center and the University of Minnesota. In this prospective observational study,17 all patients demonstrated significant HMW vWF multimer-level reductions within 30 days after LVAD implantation. An analysis of patients with different causes of heart failure has shown that no patient with normal HMW vWF multimer levels developed bleeding events,16 thus supporting the role of HMW vWF multimer loss in the development of GI tract bleeding. An important limitation of these observations is the
Angiodysplasia Formation in the Axial-Flow LVAD Population

The loss of HMW vWF multimers is not the only putative pathophysiological mechanism for GI tract bleeding shared by axial-flow LVADs and aortic stenosis. There is a strong association between aortic stenosis and the development of AVMs. One proposed mechanism suggests that increased intraluminal pressures and vascular smooth muscle contractions may lead to increased sympathetic tone, causing smooth muscle relaxation, arteriovenular dilation, and, ultimately, the development of AVMs. Another hypothesis is that intestinal hypoperfusion from reduced pulse pressure leads to regional hypoxia, vascular dilation, and subsequent angiodysplasia. In a study of 172 patients receiving axial-flow support, 31% of GI tract bleeding events were caused by AVMs, with these patients being significantly older than the other LVAD recipients. Therefore, older age may also be a contributing factor to the development of AVMs in patients receiving an assist device.

Although not investigated directly with pre- and post-LVAD endoscopy, the same mechanisms responsible for AVM formation in aortic stenosis are plausible in patients treated with axial-flow devices given the chronic low pulse pressure associated with the pump. Therefore, even in the absence of firm data, it remains feasible that acquired von Willebrand disease and the increased risk for AVMs in patients treated with axial flow LVADs likely work synergistically to increase the risk of GI tract bleeding. This is especially true because HMW vWF multimers are essential for platelet-mediated hemostasis in high shear stress areas, such as GI tract malformations and AVMs (Figure 2). Unfortunately, although modification in anti-platelet and anticoagulation regimens may mitigate some of the bleeding risk associated with angiodysplasia, the rate of development of new AVMs with continuous flow has not been well established. Therefore, it is unclear whether an isolated bleeding episode from AVMs predicts future bleeding events in either the GI tract or even the cerebral circulation. These relationships should be extensively considered when assessing the competing risks of bleeding and thrombosis in the management of the LVAD patient with AVMs.

Impaired Platelet Aggregation in the Axial-Flow LVAD Population

In addition to the loss of HMW vWF multimers and the increased risk for angiodysplasia, patients treated with axial flow LVADs also develop impaired platelet aggregation, which further contributes to the increased tendency to bleed. Klovaite et al measured the ristocetin-induced platelet aggregation of 16 patients who had recently received a HeartMate II LVAD. Of the 16 patients, 11 had impaired ristocetin-induced platelet aggregation and a history of minor and major bleeding episodes. In this study, HMW vWF levels were decreased in these patients, but activity remained within the defined normal range. Therefore, the investigators concluded that the loss of HMW vWF multimers was not solely responsible for the observed reduction in ristocetin-induced platelet aggregation. An alternative mechanism suggested by this group involved inhibition of platelet aggregation by vWF fragments generated from the breakdown of the HMW vWF multimers. The relative contribution to bleeding risk from acquired von Willebrand disease; in many of the reported studies, these assays demonstrate impaired vWF activity during LVAD support, with correction after removal of the device.

Figure 2. Mechanisms implicated in gastrointestinal (GI) tract bleeding in patients with axial-flow left ventricular assist devices (LVADs); Patients treated with axial-flow LVADS are at increased risk of developing GI tract bleeding. There are several mechanisms implicated with these increased risks. The device leads to increased intraluminal pressure and lowered pulse pressure, resulting in hypoperfusion of the intestines. These physiological changes result in an increased risk of developing angiodysplasia. These devices also decrease the high-molecular-weight (HMW) von Willebrand factor (vWF) multimer size because of excessive cleavage by the metalloprotease ADAMTS13. This results in an acquired form of vWF disease. Although not studied in detail, vWF fragments from the breakdown of HMW multimers could be involved in the inhibition of platelet aggregation. These mechanisms work synergistically to cause GI tract bleeding.
disease and impaired platelet activity has yet to be studied in detail.

Assessing Thromboembolic and Bleeding Risk

When axial-flow LVADs were initially used clinically, the potential and observed risks of pump thrombosis and thromboembolic complications resulted in recommendations for high levels of anticoagulation and antiplatelet therapy after implantation. However, balancing bleeding and thrombotic complications has become a difficult clinical dilemma, made more challenging by poorly understood individual differences in patient risk profiles. Recent studies suggest that the initial aggressive anticoagulation and antiplatelet therapy recommendations resulted in excessive bleeding risk with trivial thrombotic complications. A single-center analysis showed that the HeartMate II was associated with an extremely low thromboembolic risk and required less stringent anticoagulation. In fact, in this study, only 5% of patients had a thromboembolic event, compared with 53% of patients with a bleeding event requiring ≥2 U of packed red blood cells. Likewise, in a prospective study of 331 patients, the few thrombotic events were offset by the greater risk of hemorrhagic events. However, hemorrhagic events can be severe and may not only involve the GI tract. The reported incidence of intracranial hemorrhage with axial-flow LVADs has been as high as 0.05 events per patient-years of support and is an important cause of morbidity and mortality in VAD trials. Moreover, the devastating impact of these events requires careful consideration of the risk-benefit ratio of anticoagulation therapy. The best available evidence (in the absence of long-term follow-up) suggests that thrombotic and hemorrhagic events are minimized with dose-adjusted warfarin, targeting an INR range of 1.5 to 2.5, in addition to 81 mg of aspirin therapy. However, the optimal INR goal in LVAD-treated patients with other indications for anticoagulation, such as atrial fibrillation or prior thromboembolic stroke, is yet to be established. In the absence of firm data, we recommend more aggressive anticoagulation with a goal INR in the range of 2 to 3. Indeed, balancing bleeding and thrombosis risks will be a critical component of LVAD patient management moving forward, especially with the advent of novel anticoagulant agents.

One example of where global risk assessment is imperative in minimizing both bleeding and thrombosis risk is in the bridge-to-transplantation VAD population. From a bleeding standpoint, numerous reports suggest that repeated blood transfusions engender the development of antihuman leukocyte antigen antibodies, which may limit future candidacy for successful transplantation and increase the risk for rejection episodes. However, hemorrhagic risk must be weighed against that of a single catastrophic thromboembolic stroke, which would reduce the quality of life of the patient and possibly exclude the patient from future cardiac transplantation.

Management of GI Tract Bleeding

As evidenced by the preceding discussion, the management of GI tract bleeding in the LVAD population can be challenging for clinicians; therefore, we pose some recommendations. Because of the difficulty identifying the source of GI tract bleeding, it is recommended that a gastroenterologist be part of the clinical team managing the patient. Upper and lower GI tract endoscopy should be the standard of care to assess the site of bleeding after a hemorrhagic event. However, the source of bleeding is often difficult to ascertain with traditional endoscopic methods. In such cases, the wireless PillCam SB (Given Imaging, Ltd; Yoqneam, Israel) capsule has shown promise in identifying bleeding sources in these patients, particularly in the small bowel. Although concerns have arisen regarding the possibility of the LVAD interfering with the signal transmission from the capsule or the capsule causing LVAD malfunction, to our knowledge, no interaction between the HeartMate II and the PillCam SB has been reported. Therefore, this technology has become an important diagnostic tool in the management of GI tract bleeding, if available at the treating center; however, limited evidence exists for benefit from routine or early endoscopy if pre-LVAD endoscopy did not demonstrate a potential bleeding source. These recommendations have been included in Figure 1, which depicts an algorithm used at our institution for the evaluation of GI tract bleeding.

Future Studies

An advanced understanding of the hemostatic abnormalities associated with axial-flow LVADs is necessary to guide future interventions and therapies. An understanding of the pathophysiological mechanisms associated with heightened bleeding risk is particularly important in the absence of clearly defined clinical risk factors for bleeding or thrombosis. Furthermore, carefully conducted studies, with a focus on bleeding and thrombosis as a primary end point, should be implemented as the use of these devices increases. An intriguing study might involve prospectively exploring the role of pulsatility in axial-flow pumps and its effects on GI tract bleeding. Potential outcomes to measure would include GI tract bleeding events and changes in the HMW vWF levels. Prospective documentation of anatomic GI tract changes over time, both before and after LVAD implantation, would also be helpful to define temporal trends in AVM formation. As previously mentioned, this could also be used to stratify patient bleeding risks based on preimplantation and postimplantation GI tract pathological characteristics and to determine the burden of AVMs in the advanced heart failure population. Beyond observational analyses, a randomized trial examining bleeding and thrombosis rates in a warfarin-only group compared with a warfarin plus antiplatelet therapy group would be beneficial in modifying current anticoagulation guidelines. As we enter an era with increasing access to information, laboratory tests, and potentially other complex tests of biological signatures, we may be able to evaluate tailored approaches to anticoagulation that dynamically change during the course of treatment of patients with LVADs.

Summary

Axial-flow LVADs have become an integral tool in the management of end-stage heart failure. Consequently, nonsurgical bleeding has emerged as a major source of morbidity and mortality in this fragile population. The mechanisms responsible for these adverse events include acquired von Willebrand disease, GI tract angiodysplasia formation, impaired platelet aggregation, and overuse of anticoagulation therapy. Because of
ongoing concerns for pump thrombosis and thromboembolic events, the thrombotic/bleeding paradigm has led to a difficult clinical dilemma for those managing patients treated with axial flow LVADs. As the field progresses, advances in the understanding of the pathological mechanisms underlying bleeding/thrombosis risk, careful risk stratification, and potential use of novel anticoagulants will all play a role in the management of the LVAD patient.

Disclosures
Dr Becker served as a consultant (<$10,000) to Boehringer Ingelheim, Johnson & Johnson, Bayer, Regado, BMS, AstraZeneca, and Merck; and Dr Rogers served as a consultant (<$10,000) to Thoratec and received honoraria (<$10,000) from HeartWare.

References

Key Words: left ventricular assist devices ■ bleeding rates ■ thrombosis ■ gastrointestinal bleeding
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