Bleeding and Thrombosis in Patients With Continuous-Flow Ventricular Assist Devices

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Because of the obligate intravascular location of contemporary continuous-flow ventricular assist devices (CF-VADs), it is not surprising that bleeding and thrombosis are among the most common and feared complications of this therapy, respectively. Although strides have been made in our understanding of the pathophysiology of continuous flow, intravascular CF-VADs have been widely used only in the last few years, and a great deal remains less well known (or unknown). Outcomes have improved significantly over the past decade, but a deeper understanding of how these devices perturb the delicate intrinsic balance of bleeding and thrombosis is critical to guide therapy and to overcome the current obstacles to achieving a long-term safety profile comparable to that of mechanical prosthetic valves.

Pathophysiology

Hematologic Effect of CF-VADs

The hematologic effects of CF-VADs are of significant interest and importance and have recently been reviewed in detail elsewhere. Hemocompatibility refers to the interaction of prosthetic material with blood and can be measured in terms of impact on hematologic, inflammatory, or immunologic parameters, which has been observed clinically as significant and prolonged activation of endothelial and coagulation systems after CF-VAD implantation, including intercellular adhesion molecule, E-selectin, and tissue factor, for example. Hemocompatibility has always been a goal in pump design, along with efforts to maximize blood flow without clinically significant hemolysis, areas of stasis, turbulent flow, or retrograde flow. It has been suggested that the major complications of thrombosis, bleeding, and infection could be related to the effects of blood interaction with the VAD surface, and further optimization of surface coatings presents an appealing strategy for additional exploration. A better understanding of the impact of blood–VAD surface interactions with the presently used CF-VAD devices, however, is essential to evaluating the impact of novel designs or materials. A few recent observations have provided some insight into the impact of CF-VAD on the hematologic system. The 2 areas with the most data available are acquired von Willebrand disease and platelet activation. We also comment on preliminary findings on the potential role of microparticles.

von Willebrand Factor

The finding that has garnered the most attention is the loss of large von Willebrand factor (vWF) multimers, much like Heyde syndrome as described in patients with critical aortic stenosis. High shear stress has previously been noted to alter the 3-dimensional structure and to enhance proteolysis of the vWF by ADAMTS-13, a plausible mechanism in the setting of increased shear stress with CF-VADs (see Figure 1A). Veyradier et al noted a high rate of von Willebrand disease in patients with bleeding angiodysplasia without a VAD and proposed that this deficiency was particularly pertinent at the very high shear conditions related to these malformations. In sharp contrast to heart transplant recipients, Geisen et al first reported loss of large vWF multimers in patients supported with HeartMate II and pulsatile VADs despite amounts of vWF antigen that were comparable to that seen in heart transplant recipients (Figure 1B). Impaired collagen binding capacity and ristocetin cofactor activity, a measure of vWF factor binding to platelets, were also lower in all VAD patients. This finding has been confirmed by other groups, observed to occur within the first few days after left VAD (LVAD) implantation, and noted to resolve after LVAD explantation. In contrast to the initial report, others have found altered vWF multimers in CF-VADs but not pulsatile VADs, and altered vWF multimers have been documented after exchange from pulsatile VAD to CF-VAD. A small study of CardioWest total artificial heart implants did not find evidence of decreased large vWF multimers in the first year after implantation, but we are unaware of data after prolonged (>1 year) support or with AbioCor total artificial heart. Taken together, the flow characteristics of a CF-VAD may be a critical factor, but limited and conflicting data on the impact of pulsatile-flow devices suggest that additional factors may be operative. Patients with blood type O have been noted to have lower baseline levels of vWF compared with other blood groups, and 1 study found evidence of frequent bleeding in patients with blood group O. A similar rate was noted in patients with groups B and AB, and a study of coronary artery bypass patients did not...
find evidence of increased bleeding in patients with blood group O, suggesting that the modest difference in vWF levels associated with blood type is unlikely to be clinically significant in CF-VAD patients. Taken together, the evidence of acquired von Willebrand disease in the CF-VAD population is compelling and a key contributor to the pathophysiology of gastrointestinal bleeding. However, the fact that not all CF-VAD patients experience bleeding complications implies that other factors are also critical. Some vWF fragments may be proangiogenic, suggesting that changes in vWF not only may impaire coagulation but also may simultaneously promote angiodyplasia.22

**Platelet Damage and Activation**

The relatively nonpulsatile flow typical of CF-VAD is characterized by increased shear stress and would be expected to increase platelet activation. It is well known that mechanical forces on platelets can induce activation, much like chemical stimuli such as adenosine diphosphate or serotonin. Activated platelets change shape and are characterized by increased adhesion to exogenous surfaces and decreased resistance to aggregation. Increased platelet activation and leukocyte interaction have also been described in CF-VAD-supported patients. Platelets have markedly lower tolerance for shear stress than erythrocytes, and lysis has been reported to occur at a fraction of the threshold for erythrocytes. Damage caused by a centrifugal pump was reported by Kawahito et al, and elevated PF4 and β-TG, markers of platelet damage and activation, have been reported in the MicroMed DeBakey VAD. Accumulated damage from repeated recirculation through a CF-VAD has also been hypothesized to play a role in platelet function. A flow-induced platelet activation and cumulative damage model correlated with in vitro findings, suggesting that these theoretical consequences appear biologically plausible. Clinically, Steinlechner et al compared platelet function in 12 patients with CF-VAD (9 DeBakey, 2 HVAD, 1 Incor) and healthy controls with 4 commercially available point-of-care tests: thromboelastography, rotation thromboelastometry, the Platelet Function Analyzer-100 (Siemens USA, Deerfield, IL), and Multiplate (whole-blood aggregometry; Verum Diagnostica GmbH, Munich, Germany). All VAD patients were on 100 mg aspirin and a vitamin K antagonist with a goal international normalized ratio (INR) of 2.5 to 3.5. Platelet function under high shear was severely compromised. Abnormal ristocetin-induced aggregation was observed and was only partly attributable to low vWF activity. Shear-induced platelet activation presents a potential therapeutic opportunity, and Linneweber et al have reported attenuation of platelet adhesion in CF-VAD through local delivery of the glycoprotein IIb/IIIa receptor inhibitor TAK-029 from the pump surface. The effect of surface roughness of a device has also been demonstrated to play a role in platelet adhesion and may present another therapeutic avenue to improve clinical outcomes.

Majeed et al also studied aspirin hyporesponsiveness by whole-blood aggregometry and thromboelastography and found a high incidence of aspirin hyporesponsiveness at some point during therapy but did not find any association between aspirin hyporesponsiveness and occurrence of thromboembolic events. Only 8 of 26 patients in this study had CF-VADs, and the coefficients of variation for the assays used were very high, leaving unanswered the question of the impact of platelet function on risk of thromboembolic events. Local expertise and test availability typically play key roles in whether these tests are performed and in assay selection. The optimal assay of platelet function remains controversial, and data are currently not available to evaluate the various techniques in a large population of contemporary CF-VAD recipients with correlation to clinical outcomes of bleeding and thromboembolism. Of note, thrombocytopenia or anemia, common in CF-VAD recipients, may alter results regardless of the method used. However, a potential advantage of the Platelet Function Analyzer-100 may be testing under high shear conditions, which would be anticipated to most closely resemble the acquired vWF deficiency and platelet aggregation deficiency observed clinically.

In contrast to studies observing platelet activation, a recent study of 34 HeartMate II–supported patients (Thoratec, Pleasanton, CA) measured platelet adhesion markers (soluble P-selectin and soluble CD40L) and found no discernable changes in platelet activation regardless of length of support, antiplatelet, or anticoagulation regimen. Reconciliation with prior published work is a challenge because different
pumps and medical regimens have been used, limiting our ability to definitively integrate the available information. Deeper understanding of the impact of CF-VAD on platelets may present an opportunity to improve clinical outcomes.

Microparticles
Microparticles are small cell vesicles that are shed during cell activation and apoptosis and thought to be a key mechanism of intercellular communication; a prognostic role for cardiovascular complications has been suggested, as recently reviewed. Diehl et al recently noted significantly elevated platelet, leukocyte, and endothelial cell–derived microparticles in patients after VAD, indicating enhanced vascular inflammation and procoagulation. Additional insights into the role that microparticles play in patients with CF-VADs are eagerly anticipated.

Bleeding
Bleeding is the most common complication associated with the placement of an LVAD. In the early experience with pulsatile LVADs, as many as 50% of patients required reoperation for bleeding. The intraoperative and postoperative requirements for often extensive blood product use led to decreased right ventricular function, primarily from a cytokine-mediated increase in pulmonary vascular resistance and other well-known risks of blood transfusions such as infections. The long-term adverse effects of blood transfusions are related to the development of circulating antibodies, a phenomenon known as sensitization. As a result of these circulating antibodies, LVAD recipients are subject to increased waiting time to cardiac transplantation (with the increased waiting list mortality) and increased risk of cellular malformations, but distention of submucosal venous plexus potentially revealing previously subclinical arteriovenous malformation, has long been recognized after CF-VAD, although the more intense anticoagulation typically prescribed with CF-VADs is likely an important contributory factor. Acquired von Willebrand syndrome has been postulated as a key event. Preclinical work in a porcine model has shown that even partial left heart bypass for as little as 2 hours can lead to microvascular perfusion disturbances of the small bowel despite stable hemodynamics, suggesting that ischemia may also play a role. Evaluation of ocular choroidal blood flow with CF-LVAD found a reduction in peak systolic blood flow velocity but no change in mean flow velocity, implying normal microcirculatory perfusion.

Contemporary Estimates of Rates
Although we acknowledge the importance of meticulous intraoperative hemostasis, it should be noted that surgical techniques used are variable among different centers with equivalent results. Some preliminary reports have suggested that the avoidance of cardiopulmonary bypass for placement of LVADs may have beneficial results on postoperative bleeding, blood use, and reexploration. However, it should be noted that the added technical complexity conferred by the avoidance of cardiopulmonary bypass has significantly limited its applicability.

The practice of delayed sternal closure after LVAD placement has been advocated by some as a useful strategy in LVAD patients at high risk for bleeding. It should be noted that the risk for surgical reexploration for bleeding still exists with an open chest (albeit lower compared with primary chest closure). Furthermore, such reports of this practice do not suggest an increased risk of mediastinal infections. Delayed postoperative bleeding (>7 days after LVAD implantation) resulting in pericardial effusion requiring surgical exploration is a less common but important problem. It remains to be seen whether the current common practice of avoiding postoperative heparin and reducing the INR goal will decrease the incidence of the former event. Recent observations from the University of Arizona have found that non–kaolin-activated thromboelastographic studies may permit early anticoagulation with minimal postoperative bleeding, highlighting the continued interest in optimizing postoperative anticoagulation strategy.

Gastrointestinal Bleeding
Gastrointestinal bleeding, often resulting from arteriovenous malformation, has long been recognized after CF-VAD, and the rate of gastrointestinal bleeding appears to be markedly higher in patients with CF-VADs than in those with pulsatile VADs, although the more intense anticoagulation typically prescribed with CF-VADs is likely an important contributory factor. Acquired von Willebrand syndrome has been postulated to be a critical step in the pathophysiology, potentially revealing previously subclinical arteriovenous malformations, but distention of submucosal venous plexus from diminished pulsatility and increased intraluminal pressure has also been postulated as a key event. Preclinical work in a porcine model has shown that even partial left heart bypass for as little as 2 hours can lead to microvascular perfusion disturbances of the small bowel despite stable hemodynamics, suggesting that ischemia may also play a role. Evaluation of ocular choroidal blood flow with CF-LVAD found a reduction in peak systolic blood flow velocity but no change in mean flow velocity, implying normal microcirculatory perfusion.

A recently published series of 53 gastrointestinal bleeding episodes in 32 patients (of 172 implanted with HeartMate II) provides important data on the location of bleeding. In this study, Demirouzu et al noted 16 patients with upper gastrointestinal bleeding: 15 with lower gastrointestinal bleeding and 1 with both upper and lower bleeding. Arteriovenous malformation was identified as the source in 10 of 32 patients, and the average age was significantly higher in patients with gastrointestinal bleeding (63±7 versus 50±15
years in patients without gastrointestinal bleeding; \( P = 0.0001 \). Another smaller study in patients with CF-VADs failed to demonstrate a significant association of gastrointestinal bleeding with age.\(^{11}\)

Our approach to gastrointestinal bleeding in CF-VAD patients is summarized in Figure 2. With regard to treatment, endoscopy and pharmacological therapy with proton pump inhibitors, for example, are provided in a standard fashion. Concern over electromagnetic interference from capsule endoscopy has proven unfounded, and safe use has been reported by several groups.\(^{57–60}\) Deep enteroscopy has also been used safely in this population.\(^{61}\) A potential role of dampened pulsatility on gastrointestinal bleeding has been suggested,\(^{62}\) and it could be hypothesized that attempts to decrease pump speed to restore pulsatility, potentially by decreasing shear and mitigating the destruction of large vWF multimers, may be of benefit. Administration of epinephrine at 1 to 2 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) and octreotide as continuous infusion, subcutaneous injection twice daily, or monthly intramuscular injection has also been reported.\(^{63}\) Recombinant erythropoietin may help minimize the need for transfusions after bleeding\(^{64}\) and has been suggested to have a potential hemostatic role.\(^{65}\) Antihemophilic factor/vWF complex (Humate-P; CSL Behring, King of Prussia, PA) could be considered for refractory bleeding, although the persistent presence of the CF-VAD would be anticipated to briskly recapitulate the same fate as endogenous vWF, which may limit the duration of utility. For patients with truly refractory gastrointestinal bleeding, heart transplantation and LVAD explantation on an urgent basis may be necessary.

**Central Nervous System**

Intracranial bleeding remains one of the most feared complications after CF-VAD implantation. Fortunately, this adverse event occurs infrequently, and its occurrence in the early postoperative period may be related to cardiopulmonary bypass, which is required for VAD implantation. Published rates of hemorrhagic cerebrovascular infarction are shown in the Table.\(^{43,44,68–73}\)
The additional use of recombinant activated factor VII, as well as correction of hypothermia and acidosis, is necessary.

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with a rate of 0.19 per year. Although the immediate perioperative period is associated with a higher incidence of cerebrovascular accidents, they can also occur throughout the duration of VAD support. The standard strategy to reduce the risk of thromboembolism with CF devices has been systemic anticoagulation. Despite this strategy, the risk of thromboembolism, although lower, continues to be higher than desired. Furthermore, the risk of bleeding after VAD implantation is often exacerbated with anticoagulation. CF-VADs such as the HeartMate II have been associated with a low rate of pump thrombosis. The first design of the HeartMate II was used in a European study trial in 2001; this study was terminated early, after enrolling <10 patients, because of the high incidence of pump thrombosis related to the degree of texturing of the internal blood-contacting surfaces of the pump. The pump was redesigned, and clinical studies resumed in 2003. More than 7000 patients have now been implanted worldwide with a low incidence of thrombosis.

The current HeartMate II pump motor and associated blood tube have smooth titanium surfaces; in an effort to duplicate the excellent biocompatibility of the original pulsatile HeartMate XVE, the inlet and outlet elbows and the intraventricular cannula are textured with titanium microsphere coatings. The rationale for using textured materials for the original HeartMate XVE was that they would absorb and entrap elements from the patient’s blood to form a stable, densely adherent biological lining on the inside of the device. The resultant tissue lining, rather than the underlying biomaterials, would then form the long-term blood-contacting interface, thus obviating the need for systemic anticoagulation. Therefore, the HeartMate II has benefited from duplicating several features of the original HeartMate XVE, especially in that both confer a low thromboembolic risk. The explanation for the improved thromboembolic rate most probably has more to do with the influence of high pump flows, well-executed computational fluid dynamics modeling, and the CF nature of the device rather than with the textured surfaces alone. Such high flow is associated with reduced stasis and with an improved washing effect, resulting in a favorable impact on the risk of thrombus formation in both the device pump and the patient’s heart.

In addition to the thromboembolic risks inherent with all VADs, including the currently used CF pumps, the left ventricle in patients with end-stage heart failure is prone to the development of thrombus. Moreover, after VAD implantation, the degree of blood stasis in the patient’s heart is determined in part by the opening of the native aortic valve. At our center, we usually adjust the fixed-rate speed of the currently used CF-VADs such as the HeartMate II to maximize left ventricular decompression and to improve cardiac output, simultaneously allowing at least a 1:3 ratio of aortic valve opening. We believe this adjustment may have a favorable effect on reducing the incidence of thromboembolism associated with CF pumps.

Large single-center studies with >100 HeartMate II patients have reported a low pump thrombosis incidence of 1.6%. The destination therapy randomized trial reported a pump thrombosis incidence of 4% in the CF group compared with 0% in the pulsatile-flow group. In the HeartMate II bridge-to-

transplantation clinical trial (n=281 patients), the incidence of pump thrombosis requiring device replacement was 1%. Thrombosis in CF-VAD patients has been reported in the setting of anti-phospholipid antibody syndrome and acute HIT, but data reported to date are insufficient to determine whether the incidence of thrombosis in these populations is higher.

Pump Thrombosis

Pump thrombosis is one of the most feared complications of VAD therapy, and its diagnosis is not always straightforward. An example is shown in Figure 3; published rates are shown in the Table. It can occur early or late after VAD implantation and typically presents with increased pump power, hemolysis caused by nonlaminar blood flow, or recurrent heart failure. Echocardiography may be beneficial, although indirect evidence of thrombosis such as an increase in aortic valve opening frequency or severe mitral regurgitation is most suggestive of the diagnosis. Right heart catheterization may also reveal elevated right and left heart filling pressures. Pump exchange is generally the treatment of choice, and thrombolytic therapy is often contraindicated because of recent surgery, gastrointestinal bleeding, or cerebrovascular bleeding or infarction. Pump exchange may be performed without a sternotomy through a left subcostal approach.

Interest in percutaneous treatment strategies remains high among patients and physicians alike. Successful infusion of tissue-type plasminogen activator for CF-VAD thrombosis was initially described in 2002 with 100 mg tissue-type plasminogen activator administered peripherally. A subsequent report by Delgado et al described success with slow intraventricular infusion of tissue-type plasminogen activator at 1 mg/min. Repeated administration of thrombolytics in an individual patient has also been described, and success has been reported with systemic tenecteplase. Intracavitary thrombolitics and tirofiban have also been administered successfully in patients with centrifugal-flow devices. An example of short-term changes in power and flow is shown in Figure 4. Finally, percutaneous endovascular stabilization with balloon occlusion of the outflow graft to stop regurgi-
tation before definitive surgical replacement was possible has been reported.96

Central Nervous System
Cerebrovascular infarctions in the setting of VAD that are not due to hemorrhage are typically presumed to be thromboembolic in origin. Published rates are shown in the Table. A prior report of cerebrovascular infarctions in patients with VAD suggested increased risk with duration on support and suggested that infection may increase this risk through platelet activation.97 Unfortunately, this report was limited to a single center and predominantly pulsatile pumps. Accurate evaluation of systemic blood pressure after CF-VAD remains an area of active investigation and has limited efforts to define the impact of hypertension on the risk of cerebrovascular infarction. Aggressive anticoagulation after nonhemorrhagic cerebrovascular infarction is generally not advocated because of the anecdotally reported increased risk of catastrophic hemorrhagic transformation.

Heparin-Induced Thrombocytopenia
HIT is an uncommon but potentially life-threatening complication of heparin. Cardiac surgery in this population may be problematic because alternatives to heparin for cardiopulmonary bypass pose additional challenges98 and because most patients considered candidates for VAD do not have the luxury of waiting weeks or months for HIT antibody levels to decrease. An incidence of ≈4% was reported from a single-center VAD series using particle gel immune assay and heparin-induced platelet aggregation assay, and another center using enzyme-linked immunosorbent reported an incidence of 26%.99,100 Zucker et al85 also reported a series of heart transplantations and VAD implantations in patients with HIT. Heparin was used as the anticoagulant and during cardiopulmonary bypass for 8 VAD implantations during 2007 to 2008 with a 30-day survival of 75%. Management of HIT after VAD with direct thrombin inhibitors has been described by several centers.101–103 Voeller et al104 described successful use of plasmapheresis to acutely eliminate circulating PF4 antibodies and to permit heparin during cardiopulmonary bypass for VAD implantation, providing an attractive option for patients in whom implantation cannot be delayed.

Aortic Root
Aortic root thrombosis is relatively uncommon but has been described after CF-VAD,105,106 including in the setting of temporary devices such as Levitronix CentriMag.107,108 Prior work has suggested that blood flow in the aortic root is more stagnant with CF-VADs, particularly if the outflow graft is located in the descending aorta.109,110 The potential for this complication highlights the need for anticoagulation and may pose particular risk in the setting of permanent aortic valve closure or suboptimal aortic valve opening frequency. The impact of the presence of a mechanical aortic prosthetic valve on this risk is unclear because the number of patients described with this complication is low.111,112

Future Directions
Looking forward, there are several areas of potential progress in our efforts to reduce the risks of bleeding and thrombosis in patients with contemporary CF-VADs. The availability of oral direct thrombin inhibitors is one such opportunity. Preliminary studies in other populations have suggested an acceptable and potentially improved safety profile compared with vitamin K antagonists, but the higher risk of bleeding in CF-VAD patients coupled with the difficulty of prompt reversal of these agents must be carefully considered.

Home monitoring of anticoagulation is an appealing option for patients, and preliminary experience has been reported in the CF-VAD population.113 Despite increasing use in other patient populations, slow uptake after CF-VAD may be limited by sparse data on its safety and efficacy and the challenges surrounding reimbursement models for supervision of home vitamin K antagonist monitoring. Whether the added convenience would also translate into improved outcomes in the CF-VAD population remains to be established.

Finally, noninvasive analytics such as acoustic signature analysis may provide an opportunity to diagnose pump thrombosis earlier in the course of development, when aggressive anticoagulation may be sufficient to prevent progression and the need for surgical pump exchange.114

Conclusions
Although outcomes have improved significantly, a deeper understanding of the impact of CF-VADs on the balance of
bleeding and thrombosis is anticipated to improve outcomes further.

**Disclosures**

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