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EDITORIAL COMMENT

Are Centrifugal Ventricular Assist Devices the Answer to Reducing Post-Implantation Gastrointestinal Bleeding?*

Sheri S. Crow, MD, MSc, Daniel D. Joyce, BA

Rochester, Minnesota

Ventricular assist devices (VAD) are an effective and innovative strategy for prolonging the life of patients with end-stage congestive heart failure. However, significant rates of post-implantation nonsurgical bleeding continue to challenge the management of these patients (1). Over the last 15 years, VADs have transitioned from early pulsatile models to present-day nonpulsatile continuous-flow designs such as the axial HeartMate II (HM II) (Thoratec Corporation, Pleasanton, California) and centrifugal HeartWare (HVAD) (HeartWare Inc., Framingham, Massachusetts). Initial investigations demonstrated that pulsatile and nonpulsatile VADs had comparable outcomes with equivalent risk profiles (2). However, longer-term follow-up revealed that the newer

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generation nonpulsatile VAD recipients experienced a higher rate of gastrointestinal (GI) bleeding than their pulsatile predecessors (1). Despite these findings, the continuous-flow VAD is now the implant of choice due to its smaller size and long-term durability. The primary source of nonsurgical bleeding in continuous-flow VAD recipients is from the GI tract and nasal mucosa. Patients with severe aortic stenosis demonstrate a similar bleeding pattern, and the associated disruption in von Willebrand factor (vWF) protein is now known as acquired von Willebrand syndrome (3). vWF is a 250 kDa protein synthesized by endothelial cells and megakaryocytes that circulates in the blood in a globular form. Blood flow through areas of high sheer stress causes an unfolding of the vWF protein, exposing sites for proteolysis and cleavage by the enzyme ADAMTS 13 (4). ADAMTS 13 cleavage divides the vWF protein into smaller segments or multimers. Following this process, the total amount of vWF in circulation remains unchanged but the number of large vWF pieces known as high molecular weight multimers (HMWM) are decreased (5). Clinically, HMWM loss is associated with bleeding secondary to the decreased ability of vWF to bind collagen and platelets to achieve hemostasis. The calcific aortic valve in aortic stenosis and the VAD impeller in a heart failure patient are believed to create an environment of high shear stress that induces vWF unfolding, cleavage, and ultimately HMWM loss. Loss of HMWM following implantation of axial continuous-flow VAD has been well demonstrated (6,7).

In this issue of *JACC: Heart Failure,* Meyer et al. (7) contrasted vWF profiles for the axial flow HM II and the centrifugal HVAD. The objective was to determine whether the centrifugal HVAD design generates the same HMWM loss that has previously been described in all axial flow devices to date. In theory, the HVAD contact-free design and lower revolutions per minute (rpm) requirements (HVAD: 2,892 ± 17 rpm vs. HM II: 9,741 ± 333 rpm, $p < 0.0001$) should provide cardiac support at lower levels of sheer stress (8), thereby preserving HMWM levels. However, the findings of Meyer et al. clearly demonstrate a reduction in post-implantation HMWM (HM II: 30 ± 14% vs. HVAD: 34 ± 13%, $p = 0.09$) for all 102 patients studied, regardless of the type of device implanted. These findings suggest that although HVAD sheer forces are lower, they still reach a sufficient threshold to induce vWF unfolding leading to HMWM loss.

In addition to demonstrating HMWM loss in HVAD recipients, the comparison of axial and centrifugal flow VAD recipients in Meyer et al. (7) provides insight into the relationship between device speed and vWF derangement. Meyer et al. (7) observed that within the centrifugal HVAD group, higher speeds correlated with greater loss of HMWM ($R = -0.343$, $p = 0.015$). In contrast, there was no association between speed and HMWM levels in the axial flow HM II recipients. A sheer force of at least 500 pN is required to induce vWF unfolding and exposure of ADAMTS 13 cleavage sites (9). The results of Meyer et al. (7) raise the question of whether the lower rpm HVAD requirements generate sheer forces in a range that is close to the vWF unfolding threshold. In this scenario, subtle decreases in device rpm could reduce sheer stress to a level where not all vWF unfolds, preserving some HMWM to reduce the risk for GI bleeding. Although the difference was not statistically significant, Meyer et al. (7) did observe a trend toward lower GI bleeding rates in HVAD recipients (HVAD: $n = 6$ vs. HM II: $n = 18$, $p = 0.065$).

Evaluations of VAD hematologic profiles such as the Meyer et al. study (7) ultimately seek to identify risk factors for post-implantation bleeding so that strategies for prevention and treatment can be identified. For example, the finding of Meyer et al. (7) that vWF antigen (vWF:AG) levels are higher in axial flow recipients is significant

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From the Department of Critical Care Medicine, Mayo Rochester, Rochester, Minnesota. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

(HM II: 194 ± 74 vs. HVAD: 160 ± 58, p = 0.01) because VAD recipients with post-implantation GI bleeding events have higher vWF:AG levels than their nonbleeding counterparts (5,9). Further comparisons between axial and centrifugal VAD patients with and without bleeding that focused specifically on the relationship between device speed and vWF:AG levels would begin to test the long-standing hypothesis that speed is a modifiable risk factor for post-implantation bleeding. Investigations of this kind are critical to solving the persistent dilemma generated by our inability to understand why some patients do not bleed despite universal HMWM loss following VAD implantation. Overcoming this knowledge gap requires a systematic evaluation of subtle modifications to a variety of postulated risk factors for bleeding such as targeted mean arterial pressure and pump speed.

Unfortunately, identifying laboratory values that could differentiate bleeders from nonbleeders has been hindered by limitations in our current vWF testing methods. Traditional vWF assays such as those used in the Meyer et al. study (7), and others, are unable to discretely quantify HMWM to the degree required to reflect the impact of small changes in these levels on vWF functional ability (10). These limitations preclude the type of sensitive analysis required to detect subtle differences in hemostatic function that could predict bleeding risk. Recently, our group evaluated a new automated assay that provides a more precise measurement of the impact of HMWM loss on vWF binding activity to platelets and collagen (11). In a pilot investigation of 26 axial flow VAD recipients, patients with GI bleeding had significantly lower vWF activity levels than their nonbleeding counterparts at 30 days after implantation (9). Although promising, further validation of these findings in a larger patient group is required to identify the role of this test in the bleeding assessment toolkit.

In summary, the Meyer et al. study (7) is the first to demonstrate that despite the unique features of the centrifugal design, HVAD recipients universally exhibit the same HMWM loss that is well described in axial flow VAD recipients. Further investigation of the device, patient, and hematologic risk factors for post-implantation bleeding are essential to permit prevention and management strategies that will optimize outcomes for these patients.

Reprint requests and correspondence: Dr. Sheri Crow, Mayo Rochester, Critical Care Medicine, 200 First Street SW, Rochester, Minnesota 55905. E-mail: crow.sheri@mayo.edu.

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Key Words: bleeding ■ HeartMate II ■ HeartWare ■ left ventricular assist device ■ von Willebrand syndrome.