New Treatments for Left Ventricular Assist Device-Associated Bleeding?*

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In 2004, our program in Hannover, Germany, was among the first centers in the world gaining clinical experience with a new ventricular assist device (VAD) called the HeartMate II (HMII) (Thoratec Corporation, Pleasanton, California). At that time, hopes were not high because the pilot trial was designed to cover a 180-day bridge-to-transplant approach. There were concerns about pump thrombosis; therefore, anticoagulation protocols were maximized at that time.

Within 18 months, we learned 2 important facts for the future of VAD therapy. The good news was that many patients felt fabulous on the device, and some chose to withdraw from the heart transplant list, even though they were part of a bridge-to-transplant trial. Some patients of the very early cohorts even demonstrated the possibility to live on this device for more than 5 years. This opened the door for the use of such devices not only as a bridge but also as a definitive therapy.

The second observation was a new pattern of bleeding events: gingiva bleeds, nose bleeds, and gastrointestinal (GI) bleeding became a problem that could not be solved by modifying the anticoagulation protocol. Because the clinical picture resembled the description of Heyde syndrome in patients with aortic stenosis, we checked the von Willebrand factor (vWF) in all of our HMII patients. Indeed, all of them presented acquired von Willebrand syndrome (acvWS) 2a. In all patients, the large monomers of vWF were gone. I presented this finding during an invited presentation at the International Society for Heart & Lung Transplantation annual meeting in 2007 about our initial HMII experience.

The response at the time was skeptical, and our subsequent publication was rejected several times because of 2 questions:

1. Is there any proof that the acvWS is caused by the VAD or is there no causal evidence?
2. If acvWS is present in all HMII patients, why do some bleed and others do not?

We retested our patients when one-half of the initial cohort had received heart transplants. We were able to show that the problem was gone when the pump was removed after transplant. The acvWS remained in the second half of the group that was still on the VAD. The first question was now answered (1).

In the meantime, other groups were working on the subject and coming to similar results. The Columbia group reported on acvWS being present in all of the HMII patients tested at their institution. Importantly, they pointed out that the incidence of GI bleeding was an age-dependent process (2). Other groups, such as the Texas Heart Institute, pointed out that GI bleeding was associated with the formation of arteriovenous malformations (AVMs) in the small bowel (3).

It is a straightforward process to establish the diagnosis of acvWS, but it is much more of a challenge for a laboratory to quantify the loss of large monomers. Because quantitative analysis is usually completed in batches, we were able to compare HMII and HeartWare HVAD patients in a cross-sectional analysis.

We learned from this analysis that all patients had acvWS, and the median value for both devices was the same; however, among individuals, there was a wide variation of the degree of vWF losses (4). This could give us part of the answer to the second question. The degree of vWF degradation varies among patients, and the formation of GI AVMs, which is an...
age-dependent process, increases the risk for lower GI bleeding.

The current ideas on the interaction of vWF and continuous-flow VADs are that high shear stress to the blood within the VAD leads to a physiological uncoiling of the spherical vWF, exposing binding sites for attachment to the endothelium or to a cleaving enzyme called a disintegrin and metalloproteaseinase with a thrombospondin type 1 motif, member 13 (ADAMS-13). The response of vWF is physiological because a role of vWF is to form white clots with platelets in sites of endothelial injury and high shear environments. An example is a coronary stent thrombosis, caused by endothelial injury and high shear. The nonphysiological part of it is the constant exposure to high shearing in the VADs. Because these pathophysiological encounters were made with the use of continuous-flow VADs, the question is: When do we go from establishing pathophysiology to therapeutic interventions?

For this, the paper of Bartoli et al. (5) in this issue of JACC: Heart Failure becomes significant. First of all, they established an ex vivo model to simulate shear stress-induced degradation of vWF. This alone is a milestone to enable the search for therapeutic means. A limitation to this concept is the lack of an endothelialized circulatory system.

The lack of large monomers may be due to degradation by ADAMTS-13 or by sequestration on the endothelial surface. The interplay of both mechanisms in the presence of a VAD is unknown.

To choose the tetracycline analogue doxycycline for inhibition of ADAMTS-13 seems very reasonable because many VAD patients have been treated with this drug and so far no adverse events have been reported. However, the dose suggested by Bartoli et al. (5) was a much higher dose compared to the current use of tetracycline as an anti-infective agent, higher and only produced a 10% reduction of ADAMTS-13 activity. Is this enough?

As was discussed in the paper, inhibition of ADAMTS-13 and the loss of its physiological function may lead to thrombus formation, pump thrombosis, and thromboembolic events. Rauch et al. (6) presented a more aggressive approach by inhibiting ADAMTS-13 with a monoclonal antibody.

What may be the future role of ADAMTS-13 inhibition in VAD therapy? Because shear stress is a constant phenomenon in VAD patients, continuous inhibition by high-dose drugs or by antibodies does not seem reasonable. However, an intervention in patients with acute bleeding events may be a reasonable course of action.

What are the alternatives? In 2014, an international expert group of hematologists, molecular biologists, and clinicians met to answer this question. They found that there is no evidence-based concept at the present time for treatment of bleeding events. Withholding antithrombotic therapy is a step used in many cases, the addition of antifibrinolytic therapy can be a first-line therapy (7), and the infusion of vWF containing factor VIII concentrates may be an additional therapy. The National Heart, Lung, and Blood Institute guidelines recommend the use of such concentrates prior to surgical interventions in acvWS (8). All of these interventions carry the risk of thrombosis and are usually limited to stopping a bleeding event. In these events, ADAMTS-13 inhibition may add an additional option. “Less shear” seemed to be the requirement for the development of new VADs. The next generation of devices needs to prove if the reduction in shear stress is sufficient to mitigate this problem.

Does nonpulsatile blood flow play a role? It was suspected that nonpulsatile blood flow induces AVMs. This theory has been contradicted now by Goda et al. (9) reporting on the clinical experience with the Synergy (CircuLite, acquired by Heartware Inc., Framingham, Massachusetts) micro-pump: This VAD has been used clinically for partial ventricular support. All patients had preserved pulse but were supported with a micro pump with high shear stress. A high degree of GI bleeding was found in these patients as well. Dealing with this complex phenomenon seems to be the ultimate challenge for the future of long-term VAD therapy because bleeding and thrombosis are the limiting factors of its use.

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**REFERENCES**

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