The Development of the von Willebrand Syndrome With the Use of Continuous Flow Left Ventricular Assist Devices

A Cause-and-Effect Relationship*

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The use of ventricular assist devices (VADs) as a treatment for end-stage heart failure has increased substantially in the past 5 years, due largely to the introduction and now proven superiority of the second generation of VADs. These devices have a totally new design that returns blood to the circulation by nonphasic, continuous flow (CF), as compared with the first-generation left ventricular assist device (LVAD), which mimicked the normal left ventricular function and provided pulsatile blood flow (1). The results of recent trials have confirmed the very significant improvement in not only survival with this new design, but also significant increase in functional capacity and self-assessed quality of life (1–3). Major adverse events have also decreased significantly in comparison with the first generation of pulsatile pumps, both with historical series using the same definition (1,4) and now with direct comparison in clinical trials (1–3).

The 1 new adverse side effect associated with the CF pumps is an increase in gastrointestinal (GI) bleeding (5,6). The fact that patients using CF pumps have more GI bleeding than was seen with pulsatile VADs is in part perhaps due to the new requirement for the use of warfarin anticoagulation with the CF pumps. The most common cause of bleeding is typically the development of arteriovenous malformations (AVMs), most often found in the proximal portion of the jejunum or stomach (7,8). These lesions are often missed on routine upper and lower endoscopy and typically require newer “pill” endoscopy to visualize, but have responded to endoscopic cauterization in many cases (7,9).

The biology of the bleeding associated with CF VADs is multifactorial, but in this issue of the Journal, Uriel et al. (10) have provided a very important contribution to our understanding of a potential cause-and-effect relationship between the CF physiology and GI bleeding, and that is the development of von Willebrand syndrome, as evidenced by near-total depletion of the typical multimeric structure of the von Willebrand factor (vWF), which is a good biomarker of the integrity of the vascular endothelium. The vWF levels were part of a panel of factors that includes von Willebrand antigen, ristocetin co-factor, and the von Willebrand multimers. Their retrospective study demonstrated that all 18 patients who had documented GI bleeding while on a CF pump had near-total depletion of levels of vWF at the time of the bleed. They also found that the pre-operative levels of vWF were also almost totally depleted in a similar number of CF VAD patients at the time of heart transplantation, although none of these patients had evidence of GI bleeding at the time. Importantly, the transfusion requirement after transplantation was 2-fold higher in the CF patients in comparison with a cohort of patients who underwent heart transplantation after having been on a pulsatile LVAD. There was a large SD in the levels of vWF reported, and no clear cut point was identified in this small sample size using any of the 3 components of the von Willebrand syndrome assay that could be used to predict risk of bleeding. Perhaps more convincing is the fact that the levels of vWF returned to normal very early after the VAD was removed at the time of heart transplantation and restoration of normal pulsatile blood flow. No other coagulation factors or markers of endothelial function were measured.

There are a number of potential explanations for the development of von Willebrand syndrome in these patients, but most attention has been focused on the observation of similar AVMs that develop typically in the distal colon in elderly patients with calcific aortic stenosis (11,12). The common denominator seems to be a very low pulse pressure in both settings due to limited excursion of the stenotic aortic valve with critical aortic stenosis, and thus very narrow pulse pressure; similarly, the removal of nearly all pre-load in the left ventricle prevents the aortic valve opening in most patients with a CF pump in place. The question of why nonphasic blood flow, or very low amplitude pulsatility, would lead to AVMs in such an unusual location remains unclear. There is no vascular anatomic predisposition that would be common in all patients experiencing a GI bleed with a CF pump in place, nor in patients with aortic stenosis. We have been conditioned to believe that it is sheer stress from high turbulence and flow that generates atherosclerotic lesions. These data suggest that the integrity of the vascular endothelium, as evidenced by the expression of border proteins such as vWF, is in part dependent on the stretch and distension created by pulsatile flow. It would seem counterintuitive, however, that

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the lack of pulsatile flow alone is a cause, as the measured mean pressure is often elevated in patients with CF VADs, and the function of critical organs such as the kidney and liver, as measured by biochemical markers, has been shown to return to normal soon after CF VAD implant and remain normal for more than 6 months of follow-up (13).

One simplistic approach to address the question of the role of loss of pulsatility with CF pumps has been to slow the pump speed, thus allowing more pre-load in the ventricle and measurable restoration of a normal 30 to 40 mm Hg pulse pressure and phasic flow. To date, this has not been studied prospectively, and reports of its success in altering the frequency of clinical GI bleeding remain purely anecdotal, as warfarin anticoagulation is often stopped as well. Perhaps an equally important contribution of the Uriel study (10) is that the levels of the components of the vWF panel, especially vWF multimers, can be measured by many laboratories on a prospective or routine basis. This could potentially help to guide the level of anticoagulation used in each patient and hopefully avert GI bleeding from this cause.

One reasonable approach to test this hypothesis would be to follow the levels of vWF after a period of time with altered pump speed to allow near-total return of pulsatile blood pressure and observe whether bleeding reoccurs, or more importantly, whether the levels of vWF return to normal with pulsatile flow in the individual patient.

The single unfortunate aspect of the study (10) is that it was retrospective, and thus levels were not measured in all patients to determine whether patients with very low levels may not bleed, or more importantly, whether there is a threshold level at which the risk of bleeding goes up substantially, which could thus become a guide for adjustment of anticoagulation. The whole issue of the long-term need for anticoagulation or what level of international normalized ratio is needed to prevent pump thrombosis is unclear. There are many anecdotal reports of patients who experience significant bleeding and have had all anticoagulation stopped for months, with no apparent alteration in VAD function. It also remains unclear whether antiplatelet agents alone, such as aspirin, are all that is needed if the problem seems to be at the level of the endothelium. A significant reduction in bleeding with CF pumps would be a critical advance, especially with the intended primary expansion of VAD therapy into patients not considered candidates for heart transplant due primarily to advanced age (>65 years; so-called “destination therapy”) (3). This population is less capable of tolerating significant episodes of bleeding.

This study provides not only very important insight into the biology and likely major contributor to the GI bleeding seen with CF VADs, but it provides the basis for prospective trials designed to monitor levels of vWF in these patients. The trial design could include a randomization of patients to various treatments, such as adjustment of international normalized ratio levels based on the level of vWF, compared with a control group with more frequent monitoring without adjustment. The study could be stopped early if it became clear that most episodes of clinical GI bleeding could be averted with this monitoring. Other aspects that need to be investigated include whether aspirin alone is adequate protection from pump thrombosis, as well as evaluation of whether various levels of pulsatile flow created by VAD speed adjustment can alter the incidence of GI bleeding. Some of these studies are already underway at Columbia University, where this study was performed, but these issues merit a multicenter study to be designed and initiated, ideally by the National Heart, Lung, and Blood Institute, with more patients to confirm the findings, because this is not a problem unique to any one manufacturer.

Studies such as that by Uriel et al. (10) offer important contributions to identifying a potential cause of a common and serious adverse event, but also reveal important insight into the biology of nonpulsatile blood flow.

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REFERENCES


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