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EDITORIAL COMMENT

VAD

Why Does It Bleed?*

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When continuous flow assist devices were introduced into clinical trials, there were high hopes to develop a new therapy for end-stage heart failure due to the durability of such devices. Some skepticism was raised because of the absence of pulse and the potential physiologic changes associated with it.

It has been proven that short-term life support is possible with continuous flow pumps. But can a human being live without a pulse for years—and what is the price to pay? Meanwhile some patients have lived for 10 years or longer with a continuous flow ventricular assist device (VAD), proving that human physiology can adapt even to such unphysiologic conditions. However, a high incidence of bleeding episodes were observed that were not only a risk for the individual patient, but also jeopardized the value of this therapy because it is the most frequent cause of hospital admissions.

It became very clear in the early clinical experience that these bleeding patterns were very similar to what was reported from Heyde syndrome in patients with severe aortic stenosis: a high rate of bleeding events from mucosal surfaces and severe bleeding tendencies after trauma or surgical interventions. Indeed, it was shown by our group and many others that the acquired von Willebrand syndrome type 2a, the impairment of the large monomer of the von Willebrand factor (vWF), was present in all patients with continuous flow devices who were tested. The same pathophysiological mechanism as in aortic valve stenosis was leading to the hypothesis of degradation of the large monomer vWF by shear.

We were able to show in a cross-sectional analysis of a patient cohort implanted with continuous flow devices as a bridge to transplantation, acquired van Willebrand syndrome was present in all subjects. In a repeat analysis, the findings were returned to normal in those who had received a heart transplant and continued on those still on VAD support (1). It also became quite evident that the incidence of bleeding correlates with the age of the patient. This especially is a limiting factor when continuous flow VAD are used as a chronic (destination) therapy (2).

But why do many patients bleed and others do not? It may be helpful to ask about the role of vWF in coagulation. With platelets, vWF is creating primary hemostasis of lesions in high shear environments, such as arterial lesions. For example, the occlusion of a coronary artery stent is formed by a plug of platelets and vWF. Cardiologists prevent this primary hemostasis event by inhibition of platelet activation with various agents. In VAD patients, we add platelet inhibitors as a standard therapy to prevent pump thrombosis and embolic strokes. Thereby the primary hemostasis may be compromised even further.

In addition, it is well established that the response to platelet inhibitors is very individual and may range from complete loss of platelet aggregation to full resistance to the drug. Moreover, in a quantitative analysis we could show (3) that the degree of degradation of large monomers of vWF varies substantially even within patient cohorts implanted with the same device. In essence, this is leading to the hypothesis that the impairment of primary hemostasis is present

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in every patient with a continuous flow device, but to an individual degree.

By treating long-term VAD patients, we are blindfolded: usually we do not know the degree of platelet inhibition we cause by medication, not the degree of degradation of large monomers in a given individual and certainly not the interaction of both, the effect on primary hemostasis.

With regard to the mechanism of primary hemostasis described herein, a further element seems important to create the bleeding event: a lesion to an arterial vessel, a small arterial bleeding from mucosal injury, from an arteriovenous malformation or from an ulcer. A "2-hit" hypothesis has been postulated by some investigators: 1) the forming of mucosal vascular abnormalities; and 2) the coagulation disorder caused by acquired van Willebrand syndrome and a high level of anticoagulation by medication. Once such a bleeding event starts, the hypothesis is that it would usually be taken care of by primary hemostasis if the arterial bleeding site is small enough, but with impairment of this important mechanism, it may lead to substantial blood loss and hospitalization.

SEE PAGE 962

But is this hypothesis sufficient? It seems to explain well what we see in our VAD patients. But what about the pulseless state of continuous blood flow? Some investigators postulated to reduce the VAD support and allow the native ventricle to superimpose a pulse wave by ejection on the blood flow to prevent atrioventricular malformation and subsequent gastrointestinal (GI) bleeding. Is the continuous flow responsible for forming these malformations? So far no pathophysiological evidence has been published, but there is still concern. To shed some more light on this, the paper by Patel et al. (4), in this issue of *JACC: Heart Failure*, introduces 2 important observations: 1) that atrioventricular lesions may form during reduced cardiac output in heart failure patients; and 2) that the size of these lesions may increase during the support with a continuous flow device. We know that not only skeletal muscle perfusion, but also GI perfusion is reduced in heart failure and the body adapts to low cardiac output. The investigators remind us to focus on potential noncardiac effects of this adaptation process, including the up-regulation of serum levels of angiogenic factors. In my opinion, the most important contribution of this work is the perspective of vascular malformations due to heart failure in the mucosa and possibly in other organs, such as the brain.

But there may be additional contributing factors that are not fully established. After implantation of a VAD, function of the GI tract improves, skeletal muscles may not function in the same extent, and the patient may go from cachexia to a large weight gain in a short time frame. Sympathetic nerve tone is reduced after VAD implantation, compared with the high levels in heart failure, but remain elevated compared with healthy individuals (5). What impact does this have on mucosal perfusion?

It seems, even after more than a decade of continuous flow VAD in clinical use, the understanding of effects of continuous blood flow on perfusion and physiological changes is still poor. It would be very important to verify the findings of Patel et al. (4) in a larger patient population, because it may guide us into a direction to reduce GI bleeding, which is among the most limiting factors for medical and economical efficacy of long-term VAD therapy. To introduce the nasal mucosa as a surrogate for GI vascular changes is very attractive, but it needs validation. In addition, the suggested grading system requires acceptance by other investigators to allow for multicenter studies.

If changes of mucosal vasculature are already formed in heart failure by ischemia, such as creation of ulcers and atrioventricular malformations, it would suggest VAD support should be introduced earlier in the patient's course. In addition, the burden of this complication would be a lot less if VAD became available that work below the threshold of shear for degrading large vWF monomers (6). But do we have to go back to pulsatile blood flow to avoid this complication? In my opinion, the paper by Patel et al. (4) does not support this last hypothesis. A larger, confirmatory study may direct us either to ask for low shear devices or for a reintroduction of pulsatile devices. We may not have both in the near future.

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