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EDITORIAL COMMENTARY

Left ventricular assist device pump thrombosis: Understanding mechanisms as a key to causality

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See related article on pages 667-73.

To understand left ventricular assist device (LVAD) reliability, one must incorporate the concepts not only of mechanical reliability but also of biologic reliability. Biologic reliability combines the constraints of both design and manufacturing with the performance of the device within the biologic environment, in this case the patient with end-stage congestive heart failure. Thus not only is the design of an LVAD with its biomaterial interactions crucial to the understanding of causality for pump-related thrombosis, but the patient-related inflammatory milieu of end-stage heart failure must also be considered, along with the variability in clinical management practices.

In this issue of the *Journal*, De Biasi and colleagues, representing expertise in cardiothoracic surgery and

biomedical engineering, have proposed that LVAD pump-related thrombosis is a result of many factors, best summarized by the principles espoused by Virchow more than a century ago¹ to explain the risk of development of venous thrombosis and pulmonary embolism. De Biasi and colleagues have cleverly drawn on this construct to summarize Virchow's principles of endothelial injury, hypercoagulability, and stasis and translate that triad into device biomaterial interactions, platelet activation and aberrant flow patterns within the pump and its cannulas. De Biasi and colleagues were stimulated to address pump thrombosis according to this scientific approach by recent articles that have identified this adverse event as a problem with a rising prevalence for the HeartMate II axial-flow rotary LVAD (Thoratec Corporation, Pleasanton, Calif). But, as De Biasi and colleagues note, this problem is not exclusive to the axial-flow pumps but is also seen in the HeartWare centrifugal LVAD (HeartWare Inc, Framingham, Mass). In either case, pump thrombosis often results in the need for pump exchange, which carries its own risks of morbidity and mortality, or the need for systemic thrombolytic therapy, which with repeated use may also increase the incidence of hemorrhagic cerebral vascular events.

In a healthy individual without an implant, a balance is maintained between the coagulation and fibrinolytic systems to prevent severe blood loss during vessel puncture while also reestablishing normal blood flow to the vessel after repair. When artificial surfaces are introduced,

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however, this balance may be disrupted by the body's interaction with the foreign material, resulting in unregulated reactions that may be difficult to control. The key to understanding the propensity for the biomaterial from which the pumps are manufactured to promote platelet activation rests in the risk of platelet activation by titanium. Most rotary ventricular assist devices use a highly polished titanium alloy (TiAl₆V₄) as the blood-contacting material.² TiAl₆V₄ produces an oxide layer, which helps to make this material relatively inert to thrombus formation. The tolerance of blood to this material, however, appears to be proportional to the width of the oxide layer, which may vary in vivo; in addition, titanium without the oxide layer is potentially thrombogenic.

As De Biasi and colleagues note, the blood coagulation system is aggravated in these candidates for LVAD therapy for a variety of reasons, including the inflammatory state produced by infection. What also has to be considered, however, is the proinflammatory state in patients who are often in shock or at least on the verge of multiorgan dysfunction, which results in perioperative bleeding with the subsequent need for blood product transfusion and restriction of anticoagulation. In addition, although studies reveal that globally the international normalized ratios for these patients are generally within therapeutic range, differences in institutional practices, especially in the face of gastrointestinal bleeding or stroke, result in wide variations in management strategies. In addition, although the designs of these devices have used computed fluid dynamics to optimize rotor-induced shear stress, this stress is not totally abolished. This emphasizes the role of shear-induced platelet activation.

The final element within Virchow's triad deals with abnormal blood flow patterns. This is perhaps one of the most complex of the issues we have to address. The HeartMate II has a blood-washed bearing that depends on a minimum velocity of laminar blood flow both to cool and to lubricate the bearing interface. This rate of flow is not necessarily easily determined by the cardiac output of the device, because those flows are estimates derived from power consumption. Those estimates can, in fact, be contaminated as a result of increased resistance produced by accumulated platelet thrombus formation at the bearing site. The velocity of flow depends on many factors, which include preload (which may be effected by volume but also by right ventricular function), pump rotor speed, inflow or outflow cannula obstruction, and afterload (hypertension). Early fluid dynamic and flow visualization studies of the initial prototypes for the HeartMate II indeed identified this complex relationship, demonstrating that poor washing of the inflow bearing was predictable under conditions of suboptimal rotational speed and flow conditions that were estimated in the setting of high pump afterload, low rotational speed, and low pulsatility.³ These studies clearly demonstrated how flow changed from laminar

flow to turbulent flow, especially in the inflow region of the pump where the bearing sits.

Compounding these important issues, very nicely described within this article in the *Journal*, is the fact that best practices for implantation techniques and postimplantation medical management are disturbingly variable. Management strategies advocated in past years have included running the rotary blood pumps at lower rotational speeds to encourage longevity and competency of the native aortic valve by allowing intermittent opening. Others have suggested that levels of anticoagulation can be safely reduced below those initially suggested in the original investigational device exemption trials.⁴ Some of these efforts to manage pump flows at a lower rate were intended to encourage pulsatility in the hope of reducing the crippling incidence of gastrointestinal bleeding.^{5,6}

So indeed De Biasi and colleagues have raised important issues inherent in the mechanical design of LVADs and the biologic blood element milieu within which they are used. They have appropriately invoked the triad of Virchow to help make their case clearer. Raising these issues alone, however, is not enough to reduce the incidence of this problem. Nor are more articles simply documenting the rates of thrombosis sufficient in addressing risk mitigation. What we desperately need is more granular prospective research that addresses causality.⁷ Accurate documentation of the conditions of pump performance, and information regarding preimplantation and postimplantation management practices are critical. In addition, attempts to identify whether the pump thrombosis is related to the device, to patient factors, or to management practices for each case remains to be done. Ultimately, however, device manufacturers will need to address the fundamental biomaterial and design constraints of the current technologies and their limitations. It is to be hoped that newer designs of LVAD that are on the horizon and in current clinical trials will provide some of the answers.

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