Science for surgeons: Understanding pump thrombogenesis in continuous-flow left ventricular assist devices

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Left ventricular assist devices (LVADs) have emerged as a mainstay, lifesaving treatment option for patients with refractory heart failure, with 1- and 2-year actuarial survival rates of 80% and 70%, respectively, for the current generation of Food and Drug Administration-approved continuous-flow devices.[1] Despite this progress, continuous-flow LVADs are not without their shortcomings. One issue in particular continues to vex these devices and is increasingly garnering attention in the literature: Device thrombosis and its attendant thromboembolic complications.

After a recent article exposed an unexpected uptick in the incidence of pump thrombosis with 1 of the 2 approved durable continuous-flow pumps,[2] a flurry of studies quickly ensued that sought to better delineate the problem of LVAD thrombogenesis.[3-7] Much of this effort focuses on developing patient-level and/or device-specific predictors of thrombus formation as clotting is not inevitable with current devices. The results of such clinical endeavors will no doubt be vital to improving outcomes; however, what is often lost in these analyses is an understanding of the thrombus itself. Simple questions like, "What exactly is a thrombus?" are often taken for granted, yet, overcoming the multifactorial scourge of LVAD thrombosis demands that we understand the answers to these fundamental questions.

We therefore present a contemporary review of the basic science of thrombogenesis in the setting of LVAD support and begin by outlining how clots typically form in devices, incorporating new insights into established clotting cascades. Then, we invoke a Virchow's triad of sorts to explain the 3 fundamental determinants of pump thrombogenesis: (1) titanium's bioreactive surface acts as a nidus for platelet aggregation; (2) LVAD-induced hypercoagulability is chiefly mediated by activated platelets (APs); and (3) aberrant flow predisposes to thrombogenesis via shear-stress-induced platelet activation (SIPA), hemolysis, and stasis. In doing so, we explain how common clinical events can play out on a hemorheologic level to induce clotting. We close by reflecting on the implications of our enhanced understanding of pump thrombogenesis.

One must bear in mind that although the 3 factors we will discuss underpin many clinical mechanisms involved in clotting, they do not explain the problem in its entirety. This distinction is evidenced by the observation that the aforementioned increase in pump thrombosis appears to be dependent on implant era and by the fact that the problem seems to vary widely by center.

DEVICE THROMBOGENESIS: A PLATELET PLUG AND A FIBRIN NETWORK

The general scheme of device thrombogenesis is not unlike the hemostatic response to endothelial injury. Similar to arterial clots, device thrombi are largely platelet-derived[8]; pump thrombi begin forming when circulating APs attach to an adhesion protein (eg, von Willebrand factor [vWF] or fibrinogen) found on the blood-exposed surfaces of the titanium alloys used in LVADs (Figure 1). The platelets quickly start aggregating and, in turn, release numerous procoagulant proteins, including ADP and thromboxane A_2 (these help activate and recruit other platelets and serve to propagate the thrombogenesis).[9] As this self-perpetuating cycle of aggregation continues, the APs also begin binding to one another. Specifically, the glycoprotein fibrinogen forms crosslinks between GPIIb/IIIa receptors on neighboring platelets; the resultant conglomeration of interconnected platelets is analogous to the so-called platelet plug that is generated early during the hemostatic response to vessel injury.[9]

Almost simultaneous with these events, the local plasma concentrations of other coagulation proteins, particularly tissue factor (TF), start rising.[9] Growing research has identified the source of much of this TF to be platelet-derived microparticles (MPs)[10]; these MPs have recently been implicated in pump thrombosis and may have utility as surrogate markers of platelet activation.[11] The accumulating TF soon forms activated complexes with factor VIIa (through what is traditionally termed the extrinsic pathway); this leads to the activation of factors IX and X and then to the conversion of prothrombin to thrombin, the latter of which contributes to additional platelet activation.[9]

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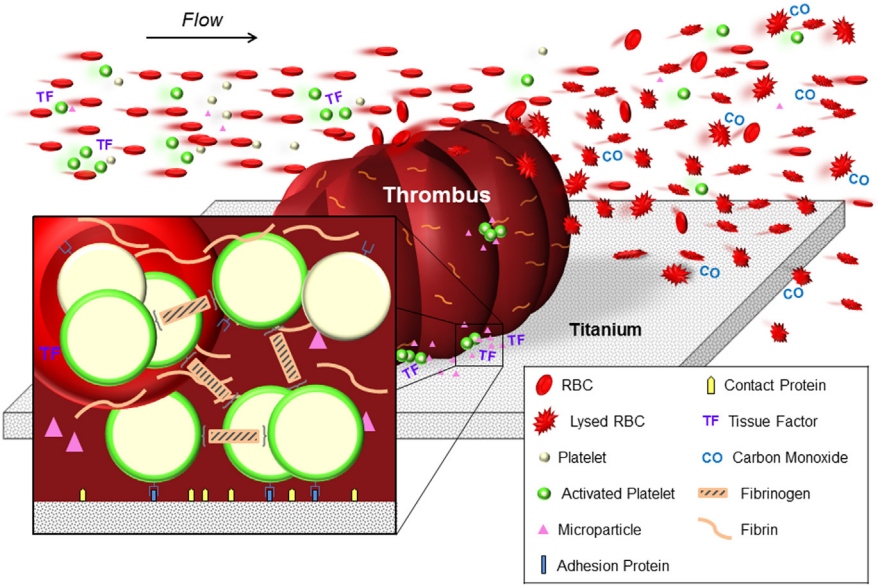

FIGURE 1. A growing pump thrombus. Shear-activated platelets adhere to various titanium-bound adhesion proteins, triggering the process of thrombogenesis. Platelet aggregation continues as neighboring activated platelets bind to each other via fibrinogen crosslinks. The release of microparticles from activated platelets increases local concentrations of procoagulant proteins, like tissue factor, that synergize with contact proteins to ultimately form a platelet-stabilizing fibrin network. The thrombus can ensnare passing erythrocytes that release carbon monoxide when lysed, further contributing to thrombus formation. *RBC*, Red blood cell.

Most notably, thrombin catalyzes the conversion of soluble fibrinogen into insoluble strands of fibrin—these strands create an interweaving fibrin network that ensnares passing erythrocytes and ultimately stabilizes the underlying platelet mass (Figure 1).[9,12] Concurrently, so-called contact proteins (notably, high molecular weight kininogen [HMWK]), which are known to adhere to devices' titanium surfaces,[13] further promote the formation of thrombin and hence, fibrin, via the intrinsic pathway.[9,12] The net result of these convergent coagulation cascades is the formation of the stabilizing fibrin network.

FUNDAMENTAL DETERMINANTS OF PUMP THROMBOSIS: VIRCHOW'S TRIAD FOR DEVICES

We have distilled the science governing pump thrombogenesis into more familiar terms—those of Virchow's triad. By way of analogy, the trio of endothelial injury, hypercoagulability, and stasis therefore becomes bioreactive material, APs, and aberrant flow, respectively, in the present context of LVAD support (Figure 2).

Although the goal of our review is to explain the basic science behind pump thrombosis, we would be remiss in not highlighting some of the key clinical contributors to device clotting as these incite the thrombogenic phenomena described herein (Table 1). A recently published review details these clinical risk factors and summarizes some of the progress our community has made thus far in lessening their contributions to thrombus formation.[7] A complementary question to the issues addressed in that article serves as the backdrop to our next discussion: On the most biophysical, rheologic level, what governs device thrombogenesis?

Bioreactive Material

As in the response to endothelial injury, LVAD thrombosis begins with a specific nidus. Whereas the exposure of subendothelial collagen (to which platelets then attach) initiates typical vessel clotting, the analogous precipitant in LVADs can be found on the devices themselves. Titanium is the most biocompatible metal at our disposal when selecting materials to be used in assist devices. That being said, titanium alloys are not completely inert; even with appropriate systemic anticoagulation and antiplatelet therapy, titanium LVADs still have some inherent thrombogenic potential.[3,4] This inescapable fact is explained by circulating platelet adhesion proteins, like fibrinogen, which (despite various surface treatments) manage to adhere to blood-exposed titanium.[14]

An article by Nielsen and colleagues[13] outlines another contributor to titanium's bioreactivity: contact-protein-mediated coagulation. As mentioned earlier, the fibrin network that lends strength to a growing thrombus evolves in response to the actions of numerous prothrombotic contact proteins (eg, HMWK, factor XII, prekallikrein, and factor XI) that make up the intrinsic pathway. Similar to platelet adhesion proteins, these contact proteins can adhere to assist device surfaces (Figure 1).[13] In so doing, contact proteins like HMWK set off a chain reaction that leads to abundant fibrin formation and additionally appear to contribute to the rate of clot growth.[13] It has also been shown that this contact protein pathway can interfere