New anticoagulant coatings and hemostasis assessment tools to avoid complications with pediatric left ventricular assist devices

Daniel C. Leslie, PhD,^a Anna Waterhouse, PhD,^{b,c} and Donald E. Ingber, MD, PhD^{d,e,f}

From the ^aFreeFlow Medical Devices, LLC, Lancaster, Pa; ^bUniversity of Sydney, Charles Perkins Center, Central Clinical School, School of Medicine, Sydney, New South Wales, Australia; ^cHeart Research Institute, Newtown, New South Wales, Australia; the ^dWyss Institute for Biologically Inspired Engineering at Harvard University; the ^eVascular Biology Program and Department of Surgery, Boston Children's Hospital and Harvard Medical School, Boston, Mass; and the ^fHarvard John A. Paulson School of Engineering and Applied Sciences, Harvard University, Cambridge, Mass.

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D.C.L. and A.W. contributed equally to this article.

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Address for reprints: Donald E. Ingber, MD, PhD, Wyss Institute at Harvard University, CLSB5, 3 Blackfan Circle, Boston, MA 02115 (E-mail: don.ingber@wyss.harvard.edu).

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Complications remain stubbornly high for pediatric patients on LVADs. © Blausen Medical Communications, Inc. License at: <https://creativecommons.org/licenses/by-sa/3.0/legalcode>. Accessed at https://en.wikipedia.org/wiki/File:Blausen_0621_LVAD.png on May 10, 2017.

CHALLENGE: THROMBOSIS AND BLEEDING

The only pediatric left ventricular assist device (pLVAD) specifically approved for use in children by the Food and Drug Administration is the EXCOR Pediatric VAD (Berlin Heart GmbH, Berlin, Germany). The EXCOR VAD gained approval on the basis of a clinical study in 2012 demonstrating significant survival benefit relative to extracorporeal membrane oxygenation in patients receiving it as a bridge to transplant.¹ The median survival time was longer than 144 days for the pLVAD, whereas it was only 10 days in the matched extracorporeal membrane oxygenation cohort. Despite this remarkable achievement, serious adverse events occurred in most study participants on the EXCOR, including infection (57%), stroke (29%), and major bleeding (46%). In the study of 48 total patients, thrombosis was observed in 43 EXCOR VADs, requiring the pump to be changed. Moreover, the recently established PediMACS registry indicates that the occurrence and type of adverse events have not changed since this pivotal trial.² These numbers highlight the central conundrum: How do we titrate anticoagulant and antiplatelet therapy when faced with concurrent thrombosis and bleeding risks?

NEED FOR BETTER CLINICAL ASSESSMENT TOOLS AND ANTITHROMBOTIC DRUGS

Managing the levels of antithrombotic agents with current clinical analysis tools is incredibly challenging in these patients. Extensive coagulopathy analysis is performed both before and after implantation of the pLVAD, and combinations of multiple anticoagulant, antiplatelet, antifibrinolytic, and procoagulant drugs are used at different stages in an

attempt to manage the thrombotic and bleeding risks.³ The types of coagulopathy analysis performed and the regimens of antithrombotic drugs used vary greatly among centers,³ and despite the use of the recommended Edmonton Anticoagulation and Platelet Inhibition Protocol in pediatric patients, there remains a stubbornly high incidence of serious adverse events, including pump change in 56% of patients, major bleeding in 43%, and neurologic events in 28%.⁴ Current clinical antithrombotic drug management is challenging for practitioners and remains ineffective for patients.

The current clinical measurements to assess platelet function and anticoagulant status include activated clotting time, activated partial thromboplastin time, partial thromboplastin time, international normalized ratio, anti-factor Xa levels, and thromboelastography⁵; however, none of these accurately predict a patient's current bleeding or thrombotic risk.⁶ New methods for real-time coagulopathy status monitoring are desperately needed for better management of antithrombotic therapies in complex situations, such as the case for patients with pLVADs. Recent promising approaches include the use of an ultrasound-based

Central Message

Improved antithrombotic surface coatings and tools to assess anticoagulation and antiplatelet function offer a potential way to reduce thrombosis and bleeding events in pediatric patients with LVADs.

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whole blood viscoelastic test that provides detailed results in approximately 10 minutes.⁶ It also may be helpful to take into account physiologically relevant hemodynamic forces and biologic components in coagulopathy analyses.⁵ For example, given that shear gradients are unavoidable in ventricular assist devices, one approach for monitoring could be a shear gradient-activated microfluidic hemostasis monitor, which evaluates coagulation and platelet activation status after a patient's blood is exposed to a series of micro-engineered stenotic arteriole-sized vessels.⁷ Interestingly, this device can be used not only in analytic laboratories but at the bedside by integrating the miniaturized microfluidic device directly into blood lines or catheters that are placed in a patient. Measurement of blood thrombosis in both static and flow environments, along with the exposure to endogenous factors or cells such as endothelium⁸ may finally give clinicians the tools needed to gauge blood dysfunction accurately in real time. Bringing these results quickly to the clinic is no small task, but they may provide critical insight that could greatly improve antithrombotic medication management.

The multiple symptoms and adverse events experienced by patients with pLVADs are a consequence of a variety of contributing factors, including the device materials, complex geometries, blood flow conditions, and drugs received. The complex interplay among these factors results in the activation and consumption of coagulation factors, activation of platelets, and the more recently recognized prevalence of acquired von Willebrand disease in patients with pLVADs.⁹ Evolving medical management therefore may include newer, more specific anticoagulant and antiplatelet drugs, such as factor XII inhibitors that inhibit material-induced thrombosis¹⁰ and phosphoinositide 3-kinase inhibitors that decrease platelet shear activation.¹¹ The ideal clinical scenario would be to match the results of these new analyses directly with specific recommendations for a targeted drug approach or a combination of drugs on a case-by-case basis.

NEED FOR BETTER DEVICES

Ultimately, we believe that better hemostasis assessment alone will not completely solve the thrombosis and bleeding problems in patients with pLVADs. Another way to prevent thrombosis and bleeding is to design better "stealth" devices that do not activate thrombotic responses, thereby limiting or perhaps one day eliminating the need for dangerous antithrombotic drugs altogether. Potentially improved implantable pLVADs currently being evaluated in clinical trials include the HeartMate 3 (Thoratec Corp, Pleasanton, Calif), the MVAD (HeartWare Inc, Framingham, Mass), and even a small (15 mm) implantable artificial heart (Jarvick Heart, Inc, New York, NY) for infants.¹² These companies have focused on improved pump design with continuous flow. We believe, however, that a focus

on improved surface coatings will further reduce the serious adverse events in patients with pLVADs.

ANTITHROMBOTIC SURFACE COATINGS

To prevent clot formation, devices are now being coated directly to prevent coagulation. The EXCOR pLVAD is coated with a CARMEDA (Carmeda AB, Upplands Väsby, Sweden) heparin-based coating, and yet thrombosis and stroke remain high despite the active anticoagulant drug immobilized directly on the surface of the pump. Surprisingly, active heparin is still bound to the surface of the device after almost a year in a patient's blood flow.¹³ This underscores the challenge in designing surfaces that prevent thrombosis; even coating the surface of pLVADs with a potent anticoagulant drug has not reduced the need for systemic administration of anticoagulants.⁴

Newer antithrombogenic coatings have been developed during the past few years that may help reduce pLVAD thrombosis in the future. A class of zwitterionic hydrophilic coatings (polymers of sulfobetaine and carboxybetaine) that are low protein binding have shown promise in reducing thrombosis on catheters in short-term dog experiments and have even gained Food and Drug Administration approval for use in catheters.¹⁴ Liquid-infused coatings¹⁵⁻¹⁷ and adherent liquid coatings¹⁸ are other promising new technologies that may reduce the need for systemic anticoagulants in patients with pLVADs. Liquid-infused coatings, such as those produced with the Slippery Liquid Porous-Infused Surfaces (SLIPS) technology (SLIPS Technologies, Inc, Cambridge, Mass) permeate a porous or roughened surface with an omniphobic liquid (eg, perfluorocarbon or silicone). A related adherent liquid coating method, tethered liquid perfluorocarbon (TLP) coatings, can be used to coat smooth surfaces of existing clinically approved medical devices. These TLP coatings consist of a liquid perfluorocarbon layer that is covalently attached to the smooth surfaces of medical devices and then overlaid with another layer of freely flowing liquid perfluorocarbon.¹⁸ These TLP coatings present a smooth liquid surface in contact with blood and prevent thrombosis by stopping the adhesion of proteins, platelets, and cells to the surface of the medical devices. Provocatively, TLP-coated arteriovenous shunts remained patent in a short-term (8-hour) study in pigs without the administration of any anticoagulants. One additional potential benefit to both polysulfobetaine and liquid coatings is their resistance to biofilm and pathogen adhesion.^{14-16,18} It is to be hoped that preliminary results demonstrating a reduction in infection rates in mice with liquid-infused coatings¹⁵ will translate into a clinical reduction in device-associated infections in the future. Ultimately, the most significant impact of these low-adhesion coatings would be to help lower the amount of thrombosis in pLVADs and to reduce the number and dose of antithrombotic

agents required to suppress bleeding events in patients with these devices.

CONCLUSIONS

With the steadily increasing use of pLVADs in children, new therapeutic avenues need to be developed to address the persistently high and varied complication rates seen clinically. There are unmet needs for improved coagulopathy monitoring, more specific anticoagulation and antiplatelet drug therapies, and improved materials and surface device coatings to reduce the disastrous thrombotic and bleeding events observed with pLVADs. With the complex nature of individual patients' profiles and device characteristics, only a combined, multifaceted approach incorporating improvements in all areas will likely lead to a major improvement in care of these desperately ill pediatric patients.

Conflict of Interest Statement

D.C.L., A.W., and D.E.I. are inventors on tethered liquid perfluorocarbon and shear-gradient-activated microfluidic hemostasis monitor patent applications. D.C.L. is employed at FreeFlow Medical Devices, LLC, which licensed the tethered liquid perfluorocarbon technology, and he holds equity in the company. D.E.I. holds equity in FreeFlow Medical Devices, LLC, and chairs its scientific advisory board. This work was supported by the Wyss Institute for Biologically Inspired Engineering at Harvard University, the Heart Research Institute, and the Discovery Early Career Researcher Award from the Australian Research Council.

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