Ventricular assist device thrombosis: Mind your P's & Q's—Pumps, patients, and pills

Patti Massicotte, MD, MSc, MHSC,^a Trevor Snyder, PhD,^b John Stulak, MD,^c and Lisa Baumann Kreuziger, MD, MS^{d,e}

From ^aKIDClot, Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada; the ^bDepartment of Research and Development, VADovations Inc, Oklahoma City, Okla; the ^cDepartment of Cardiovascular Surgery, Mayo Clinic College of Medicine, Rochester, Minn; the ^dBlood Center of Wisconsin, Blood Research Institute, Milwaukee, Wis; and the ^eDivision of Hematology & Oncology, Department of Medicine, Medical College of Wisconsin, Milwaukee, Wis.

Received for publication Aug 9, 2016; revisions received Sept 7, 2016; accepted for publication Sept 14, 2016; available ahead of print Dec 10, 2016.

Address for reprints: Patti Massicotte, MD, MSc, MHSC, Stollery Children's Hospital, 11405 87 Ave, Edmonton, Alberta T6G 1C9, Canada (E-mail: mm41@ualberta.ca).

J Thorac Cardiovasc Surg 2017;153:1503-6

0022-5223/\$36.00

Copyright © 2016 by The American Association for Thoracic Surgery

<http://dx.doi.org/10.1016/j.jtcvs.2016.09.092>

Feature Editor's Note—Despite ongoing progress in ventricular assist device therapies for end-stage heart failure in children, device-related thrombotic and hemorrhagic complications remain the major causes of morbidity and mortality in these patients. This issue appears to be exacerbated by the lack of suitable continuous-flow devices for small children, along with the unique challenges of anticoagulation strategies in the pediatric population. Dr Patti Massicotte is a recognized authority in pediatric hematology, with focused expertise in the evolving coagulation profile of children. She was an integral contributor to the only prospective ventricular assist device trial that has been conducted in children. The protocols that she has developed for anticoagulation management in children requiring ventricular assist device therapy have been widely adopted in this difficult field. Massicotte and colleagues' timely review highlights the ongoing challenges of anticoagulation management in children who require ventricular assist device therapy and provides a useful framework for future study.

Charles D. Fraser, Jr, MD

Ventricular assist devices (VADs) have revolutionized the care of severe cardiac failure in adults and children, prolonging life while increasing its quality. Potentially life-threatening adverse events, however, including hemorrhage and thrombosis, may result. In adults, increased rates of VAD-related thrombosis, including stroke and pump thrombosis, have occurred with continuous-flow (CF) left VADs (LVADs).^{1,2} Although thromboembolic events have always occurred with mechanical circulatory support devices, this concern was substantially heightened by the multicenter publication in 2013 identifying an “unexpected abrupt increase” in thrombosis with the HeartMate II LVAD

HeartMate II (Thoratec Corporation, Pleasanton, Calif) with in situ thrombosis.

Central Message

Life-threatening thrombotic complications occur with ventricular assist devices. Thrombosis prevention is dependent on pump design and on patient and clinical management factors.

See Article on page 669 in the March 2017 issue.

See Editorial Commentary page 1507.

See Editorial page 1509.

FIGURE 1. HeartMate II (Thoratec Corporation, Pleasanton, Calif) with in situ thrombosis.

(Thoratec Corporation, Pleasanton, Calif), as shown in Figure 1.³ These findings were confirmed by a larger analysis from the Interagency Registry for Mechanically Assisted Circulatory Support. An updated analysis of this registry showed that after increasing pump thrombosis from 2009 to 2013, rates in the first half of 2014 decreased.¹ The incidences of pump thrombosis at 6 months were 2% in 2009, 4% in 2011, 8% in 2013, and reduced to 5% through June of 2014. The observed thrombosis rate varied, however, by center and location (North America vs Europe). These findings indicate that a range of factors contributed to the change in the incidence of pump thrombus. HeartWare HVAD Investigators demonstrated similar increases in pump thrombosis with the HeartWare HVAD (HeartWare International Inc, Framingham, Mass),² suggesting a wider change in pump management and not only a change in device design or production.

The specific causes of VAD-related thrombosis are unknown but arise from three areas: patient-related factors, clinical management factors, and pump design factors. Patient-related factors, including age, body mass index, and sex,^{1,2} must be recognized but are not often modifiable. Clinical management factors demonstrated to contribute to thrombosis include less rigorous antithrombotic therapy management,^{1,2} pump placement and inflow cannula positioning, operating at lower speeds, and uncontrolled hypertension.² These factors were investigated in part in the Thoratec-sponsored PREVENTION of HeartMate II Pump thrombosis (PREVENT) trial to examine factors to reduce pump thrombosis events with the HeartMate II. The trial completed enrollment in February, with the results recently presented at the International Society for Heart and Lung Transplantation meeting in April 2016. Final publication will aid in determining the best evidence-based practices to reduce the incidence of HeartMate II pump thrombosis, but the initial report indicated that adherence to the implant, medical, and maintenance recommendations resulted in a reduced pump thrombosis rate. The recent decline in thrombosis may be attributed to increased antithrombotic therapy, improved blood pressure control, and changes in device design (eg, sintering the HVAD inflow cannula to prevent HVAD thrombosis), yet adverse events persist.¹ Safe and effective treatment regimens for device thrombosis are currently lacking, and existing retrospective studies suggest poor outcomes.⁴ Medical management of adult patients with HVAD thrombosis yielded hemorrhagic stroke in 21% of patients, death in 10%, and a recurrence rate of 57%.⁴ Other issues, such as adjustments of anticoagulation and antiplatelet therapy around infectious episodes and when a malpositioned inflow cannula can be managed medically or requires surgery,

remain to be elucidated. Surgical exchange successfully resolves pump thrombosis but exposes patients to another procedure. Multicenter studies systematically evaluating treatment of pump thrombosis are needed.

Several aspects of VAD design influence thrombogenicity. Bearings are the Achilles' heel of CF-LVADs and are common sites of thrombus. Mechanical bearings (as in the HeartMate II) and hydrodynamic bearings (as in the HVAD) are susceptible to heat generation and local flow recirculation. Magnetic bearings permit larger gaps, reducing shear but increasing blood element residence time, which also can be detrimental. Rotor design and gap sizes also determine shear and time exposure conditions, contributing to subsequent hemolysis, platelet activation, and acquired von Willebrand syndrome. Heat generation and the artificial pump surfaces also lead to coagulation system activation. In addition, CF-LVADs are designed for optimal performance at a single operating point. Deviations from the best efficiency point produce suboptimal flow conditions, such as flow stagnation and vortices that increase thrombotic propensity. Flow through the pump varies during the cardiac cycle, decreasing or even becoming retrograde during diastole, particularly at lower speeds or under hypertensive conditions. The ventricular interface also presents a potential hazard, resulting in nearly all durable devices adopting a sintered titanium bead interface with the myocardium; however, pannus formation in the HVAD remains a common pathologic finding.⁵ Thrombus ingestion appears to contribute to a substantial number of pump thrombosis episodes and may have contributed to the 17% neurologic event rate observed in the CE Mark trial for the "wide gap" HeartMate III device.⁶ Thorough characterization of VAD thrombotic vulnerabilities could assist in improving management approaches and identifying focuses for design improvement.

As in adults, VAD-related thrombosis occurs in children.^{7,8} Although there are many similarities, children present unique challenges when implanting and managing VADs. Infants and small children are supported with the extracorporeal, pulsatile Berlin Heart EXCOR (Berlin Heart GmbH, Berlin, Germany),⁹ which provides a substantially different hemodynamic support profile from a CF-LVAD. Device malfunction, including pump thrombosis in pulsatile LVADs, has been documented to occur in children at 6 months; however, most recorded events are with the EXCOR, for which no standardized guidelines for device exchange exist, and may be overestimates of device malfunction.⁷ CF-LVADs have been used in teenagers and recently in younger children. Device malfunction, including pump thrombosis, occurred in 16% of children implanted with a CF-LVAD, approximately double the rate associated with the same devices in adults.⁷

Examples in anatomic differences in children include the HVAD being implanted in a smaller ventricle, a morphologic right ventricle serving as the systemic ventricle in congenitally corrected transposition of the great arteries, or dextrocardia in which the outflow graft is reversed. Children requiring VADs present added challenges, including heterogeneity in the diagnoses causing heart failure and developmental differences in hemostasis.¹⁰ Children also have altered pharmacokinetics and pharmacodynamics of antithrombotic agents, which affects management after VAD implantation.¹⁰ Overall, children present a range of hemostatic and anatomic challenges, which differ significantly from those in adults with dilated cardiomyopathy who receive the same CF-LVADs.

The optimal antithrombotic regimen to prevent thrombotic complications without causing bleeding is unknown. VAD trials suggest approaches to anticoagulant and antiplatelet therapy, but dosing and therapeutic targets have not been uniform across sites and approaches have not been compared in a randomized fashion.¹⁰ In children, the EXCOR investigational device exemption study included antithrombotic therapy guidelines designed on the basis of the challenges in children.^{11,12} Despite this, stroke and major bleeding occurred in 29% and 50% of children, respectively. Building on experience from the EXCOR investigational device exemption study, the National Institutes of Health National Heart, Lung, and Blood Institute—funded The NHLBI Pumps for Kids, Infants, and Neonates (PumpKIN) Program will study a CF-LVAD in children with modified antithrombotic guidelines attempting to decrease adverse outcomes. Determining optimal use of current agents, including heparin, vitamin K antagonists, and aspirin, is needed. One important area lacking standardization for children and adults is assessment of platelet function. Patients with VAD support can have platelet activation and hyperactivity, but they may also have platelet dysfunction and impaired responses to some agonists. Antiplatelet agents are used to modulate activity; however, assessment of platelet function and either efficacy of or resistance to antiplatelet therapy is inadequate. A number of laboratory tests are available, yet each has limitations, which can yield erroneous results and potentially misguide therapy. Prothrombotic versus fibrinolytic state varies temporally in adults in response to VAD implantation, inflammation, infection, and administration of other platelet-active medications, and guidelines for frequency of long-term monitoring are needed. In children, studies are lacking to demonstrate the role of developmental hemostasis in influencing all these clinical situations. In addition, completion of clinical studies in children is challenging because of the much smaller numbers of children requiring

VADs, which affects patient recruitment and sample size. Inhibitors to contact pathway factors XI and XII have been developed but have not been tested in patients with CF-LVAD support. Short-acting antiplatelet therapies with reversibility may be a therapeutic option, especially for the early postimplantation period and during attempts to manage pump thrombus medically. Orally administered short-acting or reversible anticoagulation options would also be favored for bridge-to-transplant candidates. Although some agents are in development, there is no available agent targeting the platelet glycoprotein 1B and von Willebrand interaction, which may be involved in clot initiation or propagation. As additional anticoagulant and antiplatelet therapies become available, systematic evaluation in patients with LVAD support should be explored, although it is unlikely that a single regimen will be suitable for all VAD recipients and for all devices. Importantly, results from studies with new antithrombotic agents in adults cannot be applied to children because of developmental differences. Pediatric efficacy and safety studies are mandatory.

The initiation of prospective studies with old or newly designed VADs in children and the documented increased rate of pump thrombosis in adults underscore the need for device manufacturers, clinicians, and regulators to collaborate. The ideal LVAD will be durable, produce minimal blood trauma, and be implantable through minimally invasive approaches in a range of patient sizes, including neonates. Improved preclinical testing of blood trauma and thromboembolic risks spanning the entire device range are needed to evaluate new designs and devices before a clinical trial. Ideally, new VAD trials would confirm a comprehensive suite of preclinical testing for hemolysis, bleeding propensity, and thromboembolic resistance, rather than serve as an exploration of the device adverse event profile. In addition, national and international collaboration between pediatric and adult VAD communities should occur to allow prompt identification and addressing of problems that arise. Through analysis of robust databases, the risks and benefits of specific VADs can be provided to patients and families, allowing better informed choices about their or their child's therapy. Collaboration is necessary and urgently required to establish a standard of practice, evaluate new medical therapies and devices, and ultimately improve patient care.

Conflict of Interest Statement

P.M. is a consultant for the National Institutes of Health National Heart, Lung, and Blood Institute in the PumpKIN study. T.S. is employed by VADovations Inc. All other authors have nothing to disclose with regard to commercial support.

References

1. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Myers S, Acker MA, et al. Pump thrombosis in the Thoratec HeartMate II device: an update analysis of the INTERMACS Registry. *J Heart Lung Transplant*. 2015;34:1515-26.
2. Najjar SS, Slaughter MS, Pagani FD, Starling RC, McGee EC, Eckman P, et al. HVAD Bridge to Transplant ADVANCE Trial Investigators. An analysis of pump thrombus events in patients in the HeartWare ADVANCE bridge to transplant and continued access protocol trial. *J Heart Lung Transplant*. 2014;33:23-34.
3. Starling RC, Moazami N, Silvestry SC, Ewald G, Rogers JG, Milano CA, et al. Unexpected abrupt increase in left ventricular assist device thrombosis. *N Engl J Med*. 2014;370:33-40.
4. Saeed D, Maxhera B, Albert A, Westenfeld R, Hoffmann T, Lichtenberg A. Conservative approaches for HeartWare ventricular assist device pump thrombosis may improve the outcome compared with immediate surgical approaches. *Interact Cardiovasc Thorac Surg*. 2016;23:90-5.
5. Strickland KC, Watkins JC, Couper GS, Givertz MM, Padera RF. Thrombus around the redesigned HeartWare HVAD inflow cannula: a pathologic case series. *J Heart Lung Transplant*. 2016;35:926-30.
6. Netuka I, Sood P, Pya Y, Zimpfer D, Krabatsch T, Garbade J, et al. Fully magnetically levitated left ventricular assist system for treating advanced HF: a multicenter study. *J Am Coll Cardiol*. 2015;66:2579-89.
7. Blume ED, Rosenthal DN, Rossano JW, Baldwin JT, Eghtesady P, Morales DL, et al; PediMACS Investigators. Outcomes of children implanted with ventricular assist devices in the United States: first analysis of the Pediatric Interagency Registry for Mechanical Circulatory Support (PediMACS). *J Heart Lung Transplant*. 2016;35:578-84.
8. Rossano JW, Lorts A, VanderPluym CJ, Jeewa A, Guleserian KJ, Bleiweis MS, et al. Outcomes of pediatric patients supported with continuous-flow ventricular assist devices: a report from the Pediatric Interagency Registry for Mechanical Circulatory Support (PediMACS). *J Heart Lung Transplant*. 2016;35:585-90.
9. Fraser CD Jr, Jaquiss RD, Rosenthal DN, Humpl T, Canter CE, Blackstone EH, et al. Berlin Heart Study Investigators. Prospective trial of a pediatric ventricular assist device. *N Engl J Med*. 2012;367:532-41.
10. Baumann Kreuziger L, Massicotte MP. Mechanical circulatory support: balancing bleeding and clotting in high-risk patients. *Hematology Am Soc Hematol Educ Program*. 2015;2015:61-8.
11. Rutledge JM, Chakravarti S, Massicotte MP, Buchholz H, Ross DB, Joashi U. Antithrombotic strategies in children receiving long-term Berlin Heart EXCOR ventricular assist device therapy. *J Heart Lung Transplant*. 2013;32:569-73.
12. Steiner M, Bomgaars L, Massicotte MP. Berlin Heart EXCOR Pediatric VAD IDE study investigators. Antithrombotic therapy in a prospective trial of a pediatric ventricular assist device. *ASAIO J*. 2016;62:719-27.