

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Coagulation and Thrombotic Complications Associated With Ventricular Assist Devices

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H&O How do ventricular assist devices work?

DG Ventricular assist devices (VADs) are pumps that take over the function of the failing left ventricle and restore normal blood flow and end-organ function. For people who are in terminal heart failure, VADs are used as a way to resuscitate and stabilize them until a heart transplant becomes available. Most recently, these devices have been used as alternatives to transplantation.

Several types of VADs are clinically available or in preclinical evaluation. They can be divided into 3 generations. The first generation pumps, the so-called pulsatile pumps, are the most commonly used and have been available for approximately 20 years. The most widely utilized VADs in this category are the HeartMate (Thoratec), the paracorporeal VAD (Thoratec) and implantable VAD (Thoratec), and the Novacor pump (Baxter).

Because of the limitations of this technology—pulsatile pumps are large and noisy, and prone to infection and malfunction—a new generation of simpler, miniaturized devices has been developed. The second-generation VADs are known as nonpulsatile (or continuous) flow pumps, with the most important among them being the axial flow pumps. The 3 predominant pumps are the MicroMed DeBakey (MicroMed Cardiovascular), the HeartMate II (Thoratec), and the Jarvik 2000 (Jarvik Heart).

A third generation is currently being developed, with pumps in various stages of preclinical development. These include magnetically levitated centrifugal and axial flow pumps.

H&O What are the major complications associated with these pumps?

DG The major complications vary among the different generations of pumps. With the first-generation pumps, the main limitation is the development of infection and pump malfunction after 12–18 months of use. Although these devices are placed internally, there is a tube (drive-line) that exits the skin to connect to the battery and control systems that drive the pump. Any device or procedure that involves a line exiting the skin will be associated with a risk of infection, and this remains the Achilles' heel of this life-saving technology

The second major complication of the large pulsatile pumps is their limited lifespan. Because of the presence of several moving parts and bearings, these pumps start to fail after 12–18 months of use. Unlike replacing a pacemaker, which can be done with minimal discomfort and on an outpatient basis, replacing VAD is a major undertaking requiring major surgery.

A third major problem, more commonly associated with the second-generation non-pulsatile pumps, is the development of pump thrombus and thromboembolic events. These are likely due to the interaction of blood with foreign (mostly titanium) VAD blood-contacting surfaces.

H&O Could you discuss the pathophysiology of the thrombotic complications?

DG Understanding the pathophysiology of VAD-associated thrombotic complications means understanding what happens when blood contacts a foreign surface. In the case of VADs, the underlying pathophysiologic mechanisms have not yet been identified. The greatest limitation of this technology is our poor understanding of what happens when blood interacts with a foreign surface.

Interestingly, patients with the HeartMate device, which is the most commonly used VAD, do not experience strokes or thrombotic events except in the case of infection. The lack of thrombotic complications in this subgroup indicates that there is some unique feature in

the device's engineering that protects against the occurrence of thrombi, despite the fact that individuals with these pumps do not receive anticoagulants.

H&O What is different about the HeartMate device?

DG Studies in the early 1990s, when this device was first implanted in humans, demonstrated that the surface that is exposed to the blood, which is textured titanium, appears to encourage the formation of a biologic pseudointimal lining, greatly reducing the risk of thromboembolism. By contrast, the blood-contacting surface in all other VADs is smooth.

Investigators at Columbia University and at the Texas Heart Institute evaluated explanted HeartMate pumps and examined the blood contacting surfaces. Electromicroscopy, immunochemical, and cell-sorting experiments revealed there were cells that stained for von Willebrand factor, suggesting that endothelial cells were attaching to the device. In addition, hematopoietic pluripotent stem cells (CD34+) as well as myelomonocytic cells expressing CD14, CD15, and CD33 surface molecules were identified. It appears that the pluripotent hematopoietic cells, which have a high proliferative activity, colonize the textured surfaces, possibly contributing to a nonthrombogenic biologic neointimal.

It has also been established that patients supported with this device, while successfully sustained without systemic anticoagulation, nevertheless have evidence of activation of coagulation and fibrinolysis but these pathways appear to be balanced. In clinically relevant settings (ie, infection, inflammation), the potential for bleeding or thrombosis hence exists.

H&O How do patients with VAD-associated thromboembolic complications typically present?

DG Diagnosis of an embolic event, whether associated with a VAD or not, is usually made when a patient presents with stroke, or visceral or limb ischemia. In patients with VADs, the embolism usually originates from the device or from the left ventricle. The source of the embolus is difficult to document because the internal surfaces of the device cannot be imaged. Occasionally, transesophageal echocardiography may demonstrate thrombus within the left ventricular cavity. A pump clot can only be demonstrated at the time of pump removal (after cardiac transplantation or on postmortem examination).

With the second-generation continuous flow devices, pump thrombus, rather than embolization, is observed. In this case, the diagnosis is suspected when power and current requirements for pump function increase. These devices are relatively simple, with only 1 working part, a

rotating screw. When a clot develops or becomes stuck, the screw cannot rotate as easily, and the pump requires more energy in order for the screw to rotate. This complication is thus easier to diagnose clinically; if the pump is requiring increasing energy and power to function, most likely a clot has developed.

H&O How are VAD-associated thrombotic and embolic complications managed?

DG Patients with pulsatile pumps rarely experience pump thrombi. In these patients, embolic events are managed with increasing anticoagulation (or initiating anticoagulation, in the case of the HeartMate device). If patients receiving anticoagulation continue experiencing embolic events, an antiplatelet agent might be added. If recurrent embolism occurs, efforts are made to upgrade the patient's status on the heart transplant waiting list with the hopes of securing a new organ and removing the pump.

Patients with axial flow pumps receive anticoagulation and antiplatelet therapy routinely. Development of pump thrombus in these devices is rarely associated with distal embolization. In the event of pump thrombus formation, thrombolytic agents at low dose administered intravenously have proven to be quite effective. This approach has stemmed the need for second operations to replace the device.

H&O How are patients who do not respond to these approaches treated?

DG If a patient with a pulsatile pump who is experiencing an embolic event does not respond to anticoagulant therapy or has a recurrent event, the best approach is to upgrade the patient in the transplant waiting list. Removing the pump at the time of transplantation remains the only option to remove the source of embolization.

H&O What new directions are being explored for the management of VAD-associated thrombotic and embolic events?

DG Limited research is ongoing to advance our understanding of how the blood and blood-contacting surfaces interact to create an environment that encourages prothrombotic events. Anecdotal experience using direct thrombin inhibitors and low molecular weight heparin has been reported.

One of the main thrusts of current research is to learn how to better use the treatment approaches that we already use by directly measuring the effect. Currently, people receiving antiplatelet therapy are rarely monitored, and so it is not always possible to document that the

drugs are indeed producing the desired effect. To this end, platelet function assays and thromboelastography are now routinely being used in many transplant centers to confirm platelet inhibition and follow recipients of VAD technologies long-term.

Suggested Reading

Goldstein DJ. Worldwide experience with the MicroMed DeBakey Ventricular Assist Device as a bridge to transplantation. *Circulation*. 2003;108(suppl 1):II272-II277.

Delgado R 3rd, Frazier OH, Myers TJ, et al. Direct thrombolytic therapy for intraventricular thrombosis in patients with the Jarvik 2000 left ventricular assist device. *J Heart Lung Transplant*. 2005;24:231-233.

Bond AE, Nelson K, Germany CL, Smart AN. The left ventricular assist device. *Am J Nurs*. 2003;103:32-40.

Itescu S, John R. Interactions between the recipient immune system and the left ventricular assist device surface: immunological and clinical implications. *Ann Thorac Surg*. 2003;75(6 suppl):S58-S65.

Frazier OH, Myers TJ, Jarvik RK, et al. Research and development of an implantable, axial-flow left ventricular assist device: the Jarvik 2000 Heart. *Ann Thorac Surg*. 2001;71(3 suppl):S125-S132.

McCarthy PM. HeartMate implantable left ventricular assist device: bridge to transplantation and future applications. *Ann Thorac Surg*. 1995;59(2 suppl):S46-S51.

Spanier T, Oz M, Levin H, et al. Activation of coagulation and fibrinolytic pathways in patients with left ventricular assist devices. *J Thorac Cardiovasc Surg*. 1996;112(4):1090-1097.

Scott-Burden T, Frazier OH. Cellular linings of ventricular assist devices. *Ann Thorac Surg*. 1995;60(6):1561-1562

Spanier T, Chen JM, Oz MC, Stern DM, Rose EA, Schmidt AM. Time-dependent cellular population of textured-surface left ventricular assist devices contributes to the development of a biphasic systemic procoagulant response. *J Thorac Cardiovasc Surg*. 1999;118(3):404-413.

Rose EA, Levin HR, Oz MC, et al. Artificial circulatory support with textured interior surfaces. A counterintuitive approach to minimizing thromboembolism. *Circulation*. 1994;90(5 pt 2):II87-II91.