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Coagulation and Complications of Left Ventricular Assist Device Therapy A Primer for Emergency Nurses

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ABSTRACT

Implantation of left ventricular assist devices (LVADs) is becoming more common with the advancement of mechanical circulatory support technology and the continued insufficient number of organ donors available for heart transplantation. Modern LVADs provide a mechanically induced, nonpulsatile, continuous blood flow that drastically alters the hemodynamic and coagulation profile of patients using these devices. In addition to the risk of bleeding and thrombotic events, LVAD support can also lead to arrhythmias and infection. Although LVAD therapy can prolong life, the majority of patients will experience an adverse event following implantation and many of these complications can result in emergency department visits. By understanding the pathophysiology and management of LVAD complications, emergency nurses will be able to provide prompt and quality care for this unique patient population. **Key words:** anticoagulation, complications, HeartMate II, HeartWare, left ventricular assist device

HEART FAILURE is a chronic condition affecting more than 5.1 million Americans aged 20 years and older (Go et al., 2013). The definitive therapy for heart failure is heart transplantation. Another therapy for end-stage heart failure using left ventricular assist devices (LVADs) has grown in popularity over the last decade. In 2011,

1,949 heart transplants were performed in the United States; however, at the end of 2011, 2,035 patients remained on the heart transplant waiting list (Health Resources and Services Administration, 2011). In 2011, 1,694 LVADs were implanted at centers in the United States that provided data to the Interagency Registry for Mechanically Assisted Circulatory Support ([INTERMACS], 2012). As the prevalence of heart failure is expected to increase by 25% by 2030, the use of LVADs and the number of centers implanting them is expected to rise as well (Go et al., 2013). With increased use, it is likely that more patients with LVADs will present to emergency departments (EDs) with device-related complications.

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The first LVAD was implanted in 1966, and since then remarkable advancements have been made in the technology and management of these devices (DeBakey, 2005). Today, there are three Food and Drug Administration–approved LVADs, two of which are in routine use (see Table 1). The older device, the HeartMate XVE, used an electric pusher plate to deliver a pulsatile blood flow. This device also had artificial valves that were prone to malfunction, limiting the durability of this device. Newer devices are either centrifugal or axial flow devices and produce a consistent, continuous outflow of blood from the heart. Patients with these devices have little variation between systolic and diastolic blood pressure and no palpable pulse, making the assessment of vital signs challenging. In addition, these newer LVADs are valveless with fewer moving parts, improving their life span.

With patients commonly supported on LVADs for years, complications from the device are common. Although an LVAD is used as a life-prolonging therapy, up to 89.2% of patients with an LVAD will experience an adverse event within the first 60 days after implantation (Genovese et al., 2009). Adverse events vary depending on the device, but most are common to all current devices. Long-term complications of LVADs include bleeding, thrombotic events, infection, and ventricular arrhythmias (Ensor, Paciullo, Cahoon, & Nolan, 2011). Understanding the mechanism

behind these events will allow for prompt identification and treatment by ED personnel.

COAGULATION AND LVADs

Pathophysiology

Following device implantation, the interaction of blood with the device surface leads to endothelial cell- and tissue factor-mediated coagulation, platelet activation, and initiation of other inflammatory processes (Ensor et al., 2011; John et al., 2009; Slaughter et al., 2008). Because of this hypercoagulable state, pharmacological anticoagulation is indicated to prevent thrombotic events such as device thrombosis or embolic stroke. These events can occur at any time during LVAD support and remain a major contributor to mortality in this patient population. Within clinical trials, the occurrence of ischemic stroke alone was estimated to be between six and nine events per 100 patient-years in the HeartMate II device and 11 events per 100 patient-years in the HeartWare device (Feldman et al., 2013; Pagani et al., 2009; Slaughter et al., 2009).

In addition to their hypercoagulable state, patients may develop intrinsic coagulopathy, putting them at an increased risk for bleeding when receiving pharmacological anticoagulation therapy. The mechanical shear stress of these devices can degrade von Willebrand factor, a protein necessary for platelet activation and aggregation, leading to an acquired von Willebrand factor deficiency

Table 1. Food and Drug Administration–approved durable support left ventricular assist devices

Device	Flow Type	Indication	Recommended Anticoagulation ^a
HeartMate XVE ^b	Pulsatile	BTT, DT	None
HeartWare VAD	Continuous, centrifugal	BTT	2–3
HeartMate II	Continuous, axial	BTT, DT	1.5–2.5

Note. BTT = Bridge to Transplant; DT = Destination Therapy; VAD = ventricular assist device.

^aInternational normalized ratio goals listed are those most commonly used in clinical practice. See the text for clarification or goals as recommended by device manufacturers and mechanical circulatory support guidelines (Feldman et al., 2013).

^bNot in clinical use.

(Crow et al., 2010; Mohri, 2006). This is a major contributing factor to the increased incidence of mucosal bleeding seen in this population, most often manifesting as gastrointestinal (GI) bleeding (Suarez et al., 2011). Arteriovenous malformations (AVMs) have also been linked to GI bleeding in these patients. The AVMs resulting during LVAD support may be linked to decreased pulse pressure and increased intraluminal pressure, which can lead to angiodysplasia, smooth muscle vasodilation, and arteriovenous dilation (Cappell & Lebowitz, 1986; Crow et al., 2009). However, it is unclear whether LVAD support increases the risk of AVMs or the risk of bleeding from preformed AVMs due to platelet dysfunction and acquired von Willebrand factor deficiency (Demirozu et al., 2011; Feldman et al., 2013; Klovait, Gustafsson, Mortensen, Sander, & Nielsen, 2009). On the basis of data from the INTERMACS database and other small retrospective studies, GI bleeding occurs in around 20% of patients on continuous flow device support (Feldman et al., 2013). Although not specifically recommended by the guidelines, many centers use prophylactic proton pump inhibitors or other acid-suppressing therapies such as pantoprazole or famotidine to reduce the risk of GI bleeding. Because of the cumulative effects of pharmacological anticoagulation and intrinsic coagulopathy, patients with LVADs are also at increased risk for epistaxis, intracerebral hemorrhage, and bleeding within the chest cavity (Kurien & Hughes, 2012).

Medication management

Anticoagulants

Warfarin, in combination with aspirin, has been suggested to offer a favorable balance between bleeding and thrombosis in patients with LVADs (Rossi, Serraino, Jiritano, & Renzulli, 2012). The guidelines for mechanical circulatory support (MCS) released in 2013 by the International Society for Heart and Lung Transplantation (ISHLT) recommend warfarin with the optional addition of aspirin 81–325

mg daily (Feldman et al., 2013). Whereas aspirin can be initiated immediately following device implantation, both agents should be initiated 2–3 days following implantation when the chest tubes are removed. Warfarin exerts its anticoagulation effect through inhibition of the synthesis of vitamin K-dependent clotting factors. Because of its narrow therapeutic window, warfarin must be monitored via the international normalized ratio (INR), a standardized value derived from prothrombin time that corrects for variability between different testing techniques and reagents (Hirsh, 1991). The MCS guidelines provide device manufacturer–approved INR goal ranges, as well as additional guidance for appropriate INR ranges based on clinical study data (see Table 1; Feldman et al., 2013). An INR goal of 2–3 was targeted in most continuous flow device approval studies, such as the HeartMate II Bridge to Transplant (BTT) trial (Miller et al., 2007). However, a subgroup analysis in the HeartMate II BTT trial showed a lower rate of ischemic events than hemorrhagic events. In these patients, the risk of thrombotic events increased with an INR value of less than 1.5 whereas the risk of hemorrhagic complications increased with an INR value of greater than 2.5 (Boyle et al., 2009). Thus, in clinical practice, an INR goal of 1.5–2.5 has been used for patients with a HeartMate II device, and other small studies have confirmed the decreased risk of thrombotic events in these patients (Feldman et al., 2013; John et al., 2008; Menon et al., 2012). The MCS guidelines recommend exercising caution when targeting lower INR values because of the limited data regarding an anticoagulation in this patient population (Feldman et al., 2013). In the HeartWare BTT trial, the ADVANCE trial, a protocol recommending an INR goal of 2–3 in combination with aspirin therapy was used, but anticoagulation was institution-specific (Aaronson et al., 2012). Because of the limited data regarding an anticoagulation needed with HeartWare devices, an INR goal of 2–3 is generally used (Aaronson et al., 2012). Regardless of the device, it is important to note that many patients may

require adjustment of their INR goal range over time based on the development of adverse hemorrhagic or thrombotic events. Identifying the patient's LVAD type, history of bleeding or thrombotic events, and INR goal is important in interpreting the current INR value and other signs and symptoms at the time of ED presentation. Although many new anticoagulants are now available (rivaroxaban, dabigatran, apixiban), these agents have not been adequately studied in patients with LVADs and their use is not recommended (Feldman et al., 2013).

Antiplatelet agents

No strong recommendation exists regarding the optimal antiplatelet therapy in patients with an LVAD. The current MCS guidelines state that aspirin 81–325 mg daily may be added to anticoagulation therapy with warfarin, as this combination is seen in many case reports, small studies, and clinical trials involving continuous flow LVAD support (Feldman et al., 2013). Additional antiplatelet agents such as clopidogrel may be considered on the basis of device manufacturer recommendations and patient comorbidities. Dipyridamole, an inhibitor of platelet aggregation, was combined with warfarin and aspirin in the HeartMate II BTT trial anticoagulation protocol, but only around 50% of patients received dipyridamole (Boyle et al., 2009). Its use is currently institution-specific, but dipyridamole 100 mg three times daily has been recommended. Subsequent dose increases are based on desired antiplatelet effect and concomitant antiplatelet agents (Feldman et al., 2013). Concern for patient-specific anticoagulation and antiplatelet therapy needs following LVAD implantation has led some centers to use more complex laboratory tests that assess platelet inhibition and coagulation to guide therapy (Ensor et al., 2011; Feldman et al., 2013).

Heparin

Unfractionated heparin (UFH), an anticoagulant that inhibits thrombin through

upregulation of antithrombin III, is a mainstay of therapy as both prophylaxis and anticoagulation in many disease states (Garcia, Baglin, Weitz, & Samama, 2012). Although UFH was previously used postoperatively until patients reached therapeutic INR values with warfarin, its use following device implantation is no longer recommended unless the patient has another indication for anticoagulation. This is largely due to the increased risk of bleeding during the first few days following device implantation (Slaughter et al., 2010). Unfractionated heparin or low-molecular-weight heparin is still commonly used for deep vein thrombosis prophylaxis during inpatient stays, as an anticoagulant for a non-LVAD indication, and as part of a treatment regimen for thrombotic complications such as pump thrombosis. Providers should be aware of the risk for heparin-induced thrombocytopenia and adjust therapy appropriately if that diagnosis is confirmed (Feldman et al., 2013).

Other agents

Many patients supported by an LVAD may have complex pharmacotherapy regimens that may need to be continued during the inpatient stay. Although there is limited evidence to support the use of standard medications for heart failure such as angiotensin-converting enzyme inhibitors or β -blockers following LVAD implantation, these agents may be used either to treat patient comorbidities or to optimize chance of heart recovery (Feldman et al., 2013).

OTHER COMPLICATIONS

Arrhythmias

Ventricular arrhythmias remain a leading cause of death in patients with heart failure, and although LVADs improve oxygen delivery, they do not reverse the myocardial necrosis that leads to arrhythmias. Most patients with LVADs will also have an implantable cardioverter defibrillator (ICD), and it is important to be sure that this device is functioning properly. The use of β -blockers

in patients with LVADs may decrease ventricular arrhythmias (Zipes et al., 2006). Standard therapies for the treatment of ventricular arrhythmias remain the same as for patients without LVADs. Potassium and magnesium concentrations should be maintained in the normal range, and antiarrhythmics such as amiodarone should be used as indicated. For tachyarrhythmias that limit flow, defibrillation is indicated in the absence or malfunction of an ICD. Chest compressions are not recommended in patients with LVADs because of the risk of cannula dislodgement (Feldman et al., 2013).

Gastrointestinal bleeding and hemorrhage

Initial treatment of GI bleeding in this patient population is the same as other patients presenting with this complication. The patient's antiplatelet and anticoagulation therapy should be initially reduced or held. Reversal with coagulation factors or vitamin K must be balanced against the risk of pump thrombosis.

The ISHLT recommends that patients who present with a first episode of GI bleeding may have aspirin and warfarin restarted with careful monitoring (Feldman et al., 2013). For patients who present with recurrent episodes of GI bleeding, the use of combination antiplatelet or anticoagulation therapy should be reevaluated. Patients may have their antiplatelet agents or anticoagulants held indefinitely, or the intensity of either therapy reduced (i.e., a lower aspirin dose or lower INR goal for warfarin).

Pump thrombosis

Although bleeding events are more common in LVAD-supported patients, the risk of thrombosis is still present. The most serious complication is clot formation inside the pump itself, which can lead to peripheral arterial occlusions or embolic stroke. Patients with pump thrombosis present with symptoms of cardiogenic shock (shortness of breath, fatigue, lethargy) and low LVAD flow. Upon interrogation of the device,

patients with pump thrombus typically show increased power demands ("power spikes") to drive the clot-burdened motor. Laboratory tests such as an elevated lactate dehydrogenase or free hemoglobin level may also suggest pump thrombosis. Echocardiography is typically performed, which may or may not show a clot depending on its location. Therapy for confirmed or suspected pump thrombus typically consists of intense anticoagulation with parenteral anticoagulants (UFH, low-molecular-weight heparin). Intravenous antiplatelet agents (glycoprotein IIb/IIIa inhibitors) and thrombolytics may be added after consultation with a heart failure specialist (Al-Quthami et al., 2012; Ensor et al., 2011; Kamouh, John, & Eckman, 2012).

Infection

Infection affects 25%–50% of patients following LVAD implantation and can be categorized as an infection of the LVAD or an infection related to the presence of the LVAD (Hannan et al., 2011; Sivaratnam & Duggan, 2002; Topkara et al., 2010). Such infections may lead to longer hospital stays and increased morbidity and mortality (Sivaratnam & Duggan, 2002; Topkara et al., 2010). The externalized driveline, which provides power as well as communication to the controller unit, is the most common source of infection (Pereda & Conte, 2011). Therefore, prevention of driveline infections is paramount and requires fastidious sterile dressing application to the exit site and maintenance of the intact dressing during day-to-day activities.

Driveline infections of LVADs are typically caused by skin flora such as *Staphylococcus epidermidis*. However, other microorganisms such as *Staphylococcus aureus*, *Enterococcus* spp., gram-negative organisms, and fungus may also be present (Gordon, Quagliarello, & Lowy, 2006). Empirical treatment should be targeted against resistant gram-positive and gram-negative organisms due to repeated healthcare exposure of this patient population. Agents covering methicillin-resistant *Staphylococcus aureus*

in combination with an extended spectrum penicillin, cephalosporin, or carbapenem may be appropriate depending on patient presentation and local susceptibilities. Treatment duration may be as long as 6 weeks, and surgical debridement or suppressive antibiotic therapy may be necessary in some cases (Pereda & Conte, 2011).

CONCLUSION

As the number of patients with an LVAD increases, an understanding of the effects of the device on hemodynamics, coagulation, and cardiovascular status is vital to provide appropriate ED care. Many of the complications of LVAD support can result in medical emergencies such as bleeding, thrombotic events, arrhythmias, or infection. Because of the large number of patients who experience adverse events during LVAD support, complication management is an essential component of care, and emergency nurses are poised to assist in the prompt identification and management of these complications.

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